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Monoclonal Antibodies

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Cover: "Willowhisps," watercolor and digital, by John Teehan. John is a writer, artist, and musician from West Warwick, RI. He is currently the managing editor for Medicine & Health/Rhode Island, fiction editor for BearManor Fiction, publisher for the Merry Blacksmith Press. His work has appeared on over 100 book and magazine covers over the years. His artwork can be viewed at jdteehan.deviantart.com.

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COMMENTARIES

CONTRIBUTIONS

Special Theme: **MONOCLONAL ANTIBODIES**
Guest Editor: **Syed A. Rizvi, MD**

COLUMNS

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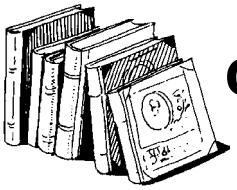

Commentaries

Research Proposal to My Readers

There are many reasons for finding clinical medicine fascinating. I am always interested in finding answers to questions that arise in everyday clinical life. I am often impressed by some new observation a patient reports, especially so if I have not seen or heard of it before. It gets me to wondering if this is some new, unreported phenomenon, and, if so, how "real" it is. Sometimes I decide to study it and may report something of value to patients and their doctors.

Recently a colleague, who was calling about something else noted that she had a patient with Parkinson's disease (PD) who not only hallucinated but maintained that she saw the same hallucinations when she looked at photos she took of the hallucinations. Had I ever encountered this? No, nor had I or some psychiatrist colleagues I contacted ever heard of it either. Then, two weeks later, a patient came into my office and told me that he was seeing people on his property taking measurements in order to put in an underground drainage system. They were wearing camouflaged outdoor gear but they were representing his town and were not hiding. He thought they were following up on a proposal to drain his land, discussed at a town meeting the year before. He said that his wife didn't believe they were real and she couldn't see them. He took photos to prove his point. In fact, the patient and wife had picked up the developed photos on their way to my office and opened the pack while talking to me. The patient scanned the photos for the first time in the office and pointed out the people he saw. They were not there, except to him. So, two cases of something I'd never seen or heard of in two weeks. How common is this phenomenon? Probably not very, but who knows?

I once gave a talk to an audience that included a multiple sclerosis (MS) specialist. I mentioned, very briefly, that PD patients sometimes complained of a sensation of tremor in parts of their bodies that couldn't shake, like their chest, or neck, or inner organs. Sometimes they feel that their limbs are shaking but when they look at them, they aren't. I then said that this occurs in people without apparent neurological problems and is not a "forme fruste" of anything. The MS neurologist came up to me and told me that this "inner tremor" is common in MS and that he had always thought it was unique to the disorder. Of course, if all you see is MS, then anything you see is going to seem like it's MS-related.

I have been wanting to study "inner tremor" for years. First I'd like merely to define its epidemiology. How common is it? Does it affect men and women equally? Does it affect old and young equally? Trying to determine whether it's related to anxiety, depression, headache, etc. would be too difficult and expensive an undertaking. But, even to define its epidemiology is no small undertaking. Ideally, one would go door to door in a community (usually in Minnesota) and have people fill out a questionnaire. More practically one could question every patient who attends a primary care office, but this too is not so easy. One needs IRB approval, and a person who can administer the questionnaire, even if it is filled out by the patient. Without IRB approval, results cannot be published in a research journal. However, I got the idea that one can bypass this obstacle, while simultaneously getting you, the reader, interested in participating in small clinical projects, to do the work for me, and to spice up your work. My plan is: any of you who are interested, can ask the next several patients you see, and it needs to be done consecutively, if at all possible, if they suffer from "inner tremor*" , and note their age, gender and whether they have a known neurological problem, specifically noting if they have a tremor**. Then, when you have results for 10 or 20 patients, e mail the results to me with your name, if you like, and your medical area (family practice, cardiology, psychiatry, etc). I will then publish the result in another one of my op/ed columns. The result would therefore not be a research publication, but an op/ed piece.

I have three goals. One is to learn something about inner tremor and educate our medical community. The second is to excite the interest of some readers in the general idea that one can pursue interesting and useful research ideas, and that these make our practice a lot more interesting. The third is to learn if one can actually obtain useful data by asking a cohort of doctors to pitch in, kind of like using Survey Monkey.

Let me know at joseph_friedman@brown.edu.

– Joseph H. Friedman, MD

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Correspondence

e-mail: joseph_friedman@brown.edu

* Inner tremor: a sensation of a part of the body tremoring, possibly a limb, that feels like it's shaking but isn't, or possibly a part of the body, like one's inner organs, that cannot actually shake. This may be present intermittently.

** Tremor: an observed regular oscillation of a body part, either at rest, or on holding a sustained posture, or with movement.

The Solemn Lady with the Lantern

Our heroes, with the passage of time, become increasingly heroic. What had been exemplary behavior is transformed, after centuries, into legendary performance; and appropriate esteem is then replaced by inappropriate worship. Thus, our credulous children are taught that our past leaders had been faultless, fearless and without blemish. Saying that many of the founders of this nation were slave-holders or religious bigots, for example, is now tantamount to heresy.

Consider one of the great heroes of Great Britain, a woman of great wealth and privilege, who exploited her position in British society to advance the health of its citizens more effectively than a battalion of contemporary physicians and surgeons.

Her childhood, as viewed in retrospect, was enriching and fulfilling. She traveled extensively, visiting such places as Egypt and the many nations of Europe. Her education, which was intensive, was supervised by her father who taught her Latin, Greek, Italian and German, as well as a rigorous training in mathematics which served her well in later years.

Nursing in the early decades of the Victorian Era was not yet a profession; indeed, in contemporary government statistics it was listed as a lower form of domestic help. To be called a nurse in the London of 1850 was to be disparagingly labeled as a vagrant, an alcoholic or a prostitute. Nightingale's interest in nursing met with her family's opposition and hence she delayed her entrance into this nurturing calling until age 33 and only after covert apprenticeships in both Germany and France.

1854 was the year that Britain and France entered into an ill-advised military venture called the Crimean War. It was a conflict ennobled by heroic poetry (such as Tennyson's 1854 paean to the suicidal "Charge of the Light Brigade"), appalling mortality rates and the inept military leadership of Lord Raglan.

With 38 recruited nurses, she volunteered her services to Britain's War Office, and she was promptly shipped off to the Turkish town of Scutari. Her inspection of the military hospital facilities revealed an incredibly filthy, vermin-infested venue, a lack of the most fundamental of facilities and a hospital mortality rate of about 42%. Her great administrative skills changed these "death houses" into efficiently managed, sanitary resources with mortality rates well below 10 %. Her corrective actions caught the attention of the world press and many poems (such as Longfellow's 1857 tribute to her: "…a lady with a lamp, I see") were generated in her honor.

And so, Florence Nightingale has entered history as a gentle nurse, an angelic soul wending from bedside to bedside, with her lantern, bringing a nurturing compassion to dying recruits, with little mention devoted to her extraordinary accomplishments beyond the Crimean interlude.

Nightingale had returned to her London home in 1856 and lived, virtually as recluse, until her death in 1910. And while she rarely left her bed chambers, she had a steady succession of visitors and her subsequent achievements in enhancing the health of Britons are truly legendary. But it was not her gentility or nurturing nature that furthered her social agenda. Rather, it was her hard-nosed insistence and reliance upon the inflexible realities of health statistics that overcame the resistance to her plans. And her opposition? Much of Parliament, the senior military establishment and even humanitarians such as Charles Dickens who were offended by her assertiveness and her reliance upon cold statistics rather than congenial anecdotes.

Of her many allies and supporters, there was William Farr (1807 – 1883) born in poverty, educated as a physician and ultimately director of Britain's General Registry Office, the agency that gathered data on births, deaths and reportable illnesses. A professional friendship ensued, a political alliance based upon their shared belief that numbers, vital statistics, have incalculable merit when applied to society's problems. And so epidemiologic studies of the successive cholera epidemics of London offered conclusive evidence that the disease was water-borne (and not air-borne) giving additional evidence to the controversial germ theory of disease.

Nightingale exploited Farr's data to prove the incompetency of Britain's health care system, both civilian and military. And in a Victorian Age when women were assigned solely to maternal and domestic tasks, Nightingale managed to create Britain's first professional college of nursing (at St. Thomas' Hospital), a new medical school solely for the military, a commission that thoroughly revised health care standards for the military, both in the field and in barracks; and perhaps her greatest achievement: transforming nursing from a menial task to a noble profession.

– Stanley M. Aronson, MD

Stanley M. Aronson, MD is dean of medicine emeritus, Brown University.

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The author and his spouse/significant other have no financial interests to disclose.

Correspondence

e-mail: SMAMD@cox.net

Monoclonal Antibodies: an Introduction

Syed A. Rizvi, MD

Monoclonal antibodies (MCA) are antibodies that are identical and derived from one type of immune cell, each a clone of a single parent cell. The extraordinarily specific nature of these antibodies is what makes MCA unique and opens up the possibilities of revolutionary applications including targeted therapy and other diagnostic applications (such as pregnancy test and testing for acquired immune deficiency syndrome (AIDS). MCA have dramatically changed how we think about and treat autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and multiple sclerosis (MS).

The concept of a "magic bullet" has been around for greater than a century. In 1900, Paul Ehrlich, a Nobel laureate, suggested that it may be possible to create a compound which can target diseased cells specifically. His life and achievements were depicted in the 1940 academy award nominated movie, "Dr. Ehrlich's magic bullet," which focused on arsphenamine, his cure for syphilis. Although the concept of a magic bullet was a straightforward one, it would take several more generations to be able to target specific cells with pinpoint precision at a cellular level. The credit for inventing monoclonal antibodies goes to George Kohler and Cesar Milsten. In 1975 both received a Nobel Prize for the discovery. In 1988 Greg Winter pioneered the technique to humanize monoclonal antibodies.

Monoclonal antibodies were typically produced by fusing myeloma cells with splenic cells from a mouse which was immunized against a particular antigen. Mouse antibodies, being slightly different from human antibodies, produced an inflammatory reaction when injected into humans, resulting in infusion reactions and the production of neutralizing antibodies which would render the MCA useless in a small percentage of patients. In order to overcome these difficulties various different kinds of approaches have been used, leading to the production off chimeric (partly mouse and partly human) and fully humanized antibodies.

Treatment with monoclonal antibodies does not usually result in a "cure". Unlike antibiotics, which have the ability to eliminate pathogens, and thus result in a cure, MCA are designed to target and modulate specific immune pathways. Discontinuation of treatment with an MCA may result in re-occurrence of disease activity.

Greater than 20 monoclonal antibodies have been approved by the FDA and are being increasingly used to treat autoimmune and neoplastic disorders. With recent improvements in techniques involved in the production of MCA, the stage is set for science to take yet another leap forward. Greater than 200 monoclonal antibodies are currently in development or are awaiting FDA approval.

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Syed Rizvi, MD, is an Associate Professor of Neurology and Director of the Rhode Island Hospital Multiple Sclerosis Center.

Correspondence

Syed A. Rizvi, MD
Neurology Foundation Inc.
2 Dudley St Ste 555
Providence, RI 02905
phone: (401) 444-3032
fax: (401) 444-2838
e-mail: SRizvi@Lifespan.org

Complications of Monoclonal Antibody Therapy

Karl Meisel, MD, and Syed A Rizvi, MD

Monoclonal antibodies (MCA) are an increasingly important class of drugs for treating autoimmune and neoplastic disorders. They have been associated with a variety of adverse events which will be discussed in this paper.

Infusion Reactions

An infusion reaction may range from mild to lethal. The severity is given a rating on a scale of one (mild) to five (lethal). Most often the signs and symptoms are mild (grade one or two). Common signs and symptoms include fever, flushing, rigors, chest discomfort, abdominal pain, nausea, vomiting, diarrhea, and rashes. Rarely, MCAs can cause anaphlaxis.[1] It may be initially difficult to distinguish a mild reaction from anaphylaxis. However, the presence of respiratory changes and urticaria are more specific to anaphylaxis and in contrast, myalgias are more likely to accompany a mild reaction. A generalized symptomatic response to infusion of MCAs typically occurs within the first two hours, but may be delayed up to 14 days after treatment. The highest risk of a reaction is during the first or second exposure to the MCA. The risk declines with repeated exposure, but 10-30% of reactions occur beyond the first two doses.[2] MCAs most associated with early infusion reactions are infliximab, rituximab, gemtuzumab, alemtuzumab, trastuzumab, cetuximab, ofatumumab.

Prevention of mild infusion reactions with premedication is routine; however, anaphylaxis may still occur. Commonly prescribed premedication regimens are diphenhydramine and acetaminophen. A patient with a mild reaction should temporarily stop the infusion, and receive symptom relief using an IV antihistamine with oral acetaminophen. They may be re-challenged at a reduced infusion rate (50%) after symptoms have resolved. If a patient develops repeated mild reactions then a referral to an allergy specialist for a desensitization protocol may be considered. A patient with a severe response consistent with anaphylaxis should not be re-challenged.

Initial management of suspected anaphylaxis is to stop the infusion. Then intramuscular injection of epinephrine should be given while support is called. If there is no pulmonary contraindication the patient is placed in a supine position, given supplemental oxygen, and a safe airway should be maintained. Volume resuscitation, intravenous antihistamines, and bronchodilators may be administered.[3]

Common signs and symptoms include fever, flushing, rigors, chest discomfort, abdominal pain, nausea, vomiting, diarrhea, and rashes.

Infectious Complications

Since monoclonal antibodies modulate the patient's own immune function, latent infections represent a serious threat. Latent infections like herpes zoster may manifest in the immunocompromised state induced by monoclonal antibodies. TNF-alpha inhibitors commonly used to treat inflammatory conditions like rheumatoid arthritis or seronegative spondyloarthropathies are associated with increased risk of latent **tuberculosis (TB)**. Therefore, when using TNF-alpha inhibitors such as infliximab, adalimumab, golimumab the patient should undergo a chest x-ray and placement of **purified protein derivative (PPD)** before initiating therapy.[4]

Agents targeting B-cells like rituximab are associated with reactivation of latent hepatitis B and JC virus infections (causes progressive multifocal leukoencephalopathy, PML).[5] Natalizumab, a MCA that inhibits leukocyte migration has been associated with over 100 cases of PML. Natalizumab was marketed for treatment of relapsing remitting **multiple sclerosis (MS)** and in post-marketing surveillance it was found to be associated with an increased incidence of PML. The risk of developing PML is one in a thousand for patients on therapy for 18 months.[6] It is rare to develop PML in the first 12 months of natalizumab therapy.[7] Initially it was believed that prior exposure or concurrent use of other immunosuppressive agents in MS patients led to the development of PML, but it is now clear that natalizumab alone increases the risk of PML. PML may cause encephalopathy, ataxia, visual field loss, diplopia, paresis, and seizure.[8] Brain CT studies typically reveal bilateral hypointense signal changes in the white matter in a patchy or confluent pattern. MRI findings include lesions that are T1 hypointense, T2 hyperintense and do not enhance or cause mass effect.[9] Early discontinuation of natalizumab and treatment with plasmapharesis may result in improved survival. Patients withdrawing from natalizumab may develop **Immune Reconstitution Inflammatory syndrome (IRIS)** and remain at significant risk of developing a severe relapse.

Infliximab, a MCA against TNF-alpha, was shown to have an adjusted relative risk of three (95% CI 1.8 to 5.1) for moderate to severe infection when compared to standard anti-rheumatic drugs.[10] Listeriosis represents a serious opportunistic bacterial infection from contaminated food that can lead to meningoencephalitis or septicemia at a higher rate in patients treated with infliximab.[11] The increased incidence of opportunistic fungal infections with histoplasmosis, coccidiodomycosis, blastomycosis in patients on MCAs targeting TNF-alpha led to a 2008 Food and Drug Administration warning. Concerning signs and symptoms are fever, lethargy, dyspnea, diaphoresis, cough, and chest x-ray with pulmonary infiltrates.[12] The risk of opportunistic infections is higher in patients on additional immunosuppressive agents, those who recently started treatment, older age, and patients with co-morbid pulmonary disease. In high risk patients, pneumo-

cystis carinii (jiroveccii) prophylaxis with **trimethoprim-sulfamethoxazole** (**TMP-SMX**) should be considered.[13] All patients treated with OKT3, a MCA targeting T cells, should be placed on TMP-SMX and ganciclovir to prevent PCP and CMV infection respectively.[14] In addition, live vaccines should not be given during treatment with MCAs.

Pulmonary Complications

Specific MCAs are associated with an increased risk of direct **interstitial lung disease** (**ILD**). Symptoms of ILD are high fever, dyspnea, and cough. Patients who develop these symptoms require discontinuation because of the potentially lethal consequences.[15] Patients should be treated with glucocorticoids after infectious etiologies are excluded by obtaining cultures and perhaps bronchoalveolar lavage. Empiric antibiotics against atypical pathogens can also be used to reduce secondary infection. ILD is reported with the use of rituximab in about eight percent of patients, and rarely in those treated with trastuzumab for breast cancer.[16] Studies of cardio-pulmonary toxicity with these agents have found increased risk in those patients on adjunctive chemotherapy agents such as **CHOP** (**cyclophosphamide, doxorubicin, vincristine plus prednisone**), anastrozole, or anthracycline/cyclophosphamide compared to MCA monotherapy.[17] Patients treated with MCAs targeting epidermal growth factor receptors used in colorectal cancers (cetuximab and panitumumab) are also known to rarely cause pulmonary toxcitiy.[18]

Hematologic-Oncologic Complications

The use of MCA may increase the risk of future malignancies. MCAs that target TNF-alpha were found in post marketing safety analysis to be associated with an OR 3.3 of malignancies (95% CI 1.3-3.1). This evidence led to an FDA warning for adults and children using TNF-alpha inhibitors. There is conflicting evidence whether all malignancy risk is truly elevated when compared to patients with **rheumatoid arthritis** (**RA**) instead of the general population. However, there is substantial evidence that the use of TNF-alpha inhibitors confers an increased risk of lymphoma.[19]

Patients taking MCAs do not commonly complain about neurologic difficulties which are typically not serious and include headaches, myalgias, and dizziness.

Blood dyscrasias are common side effects of many MCAs. Since hematologic malignancies themselves can cause similar effects as the MCAs used to treat them evidence of a direct relationship is often uncertain. However, in the setting of an autoimmune hematologic abnormality the etiology is likely the MCA. Occasionally, these hematologic effects can be life threatening. During a trial of alemtuzumab for multiple sclerosis a patient died from idiopathic thrombocytopenic purpura. Patients taking this medication should be monitored with frequent platelet counts while on treatment and should discontinue alemtuzumab if they develop evidence of autoimmune hematologic toxicity.[20] Infliximab and rituximab are also hematologically toxic, causing leukopenia, neutropenia, thrombocytopenia, and pancytopenias. Patients typically become neutropenic within the first three to six months of starting therapy. The treatment begins with withdrawal of the offending medication. For the patient who is febrile, cultures should be obtained and broad-spectrum intravenous antibiotics started. If a patient requires a blood transfusion they should only receive irradiated blood products. The efficacy of granulocyte colony-stimulating factor administration to improve blood dyscrasias is uncertain, but remains a therapeutic option. .

Neurologic Complications

Patients taking MCAs do not commonly complain about neurologic difficulties which are typically not serious and include headaches, myalgias, and dizziness. However, rare complaints include paresthesias and peripheral neuropathies. Cetuximab, a MCA targeting epidermal growth factor used in head/neck cancer and colorectal cancers, rarely can cause aseptic meningitis. In addition, cetuximab and panitumumab can cause hypomagnesemia that is manifested clinically as cramps and fatigue.[17]

More serious neurologic side effects of headache, seizure, encephalopathy and blindness may indicate that the patient has **posterior reversible encephalopathy syndrome** (**PRES**). PRES is associated rarely with bevacizumab, a MCA against vascular endothelial growth factor, used in glioblastoma, colon, lung and breast cancers.[21] The likely etiology of PRES is endothelial dysfunction leading to vasogenic edema. This can be seen on head CT as bilateral posterior hypodensities. PRES is often seen in patients with hypertension, but not necessarily malignant hypertension. Aggressive treatment of hypertension and removal of the offending agent is the recommended management strategy. In addition, even in the absence of PRES, bevacizumab is associated with an increased risk of thromboembotic stroke. (RR 1.31 [95% CI 1.08-1.6]) and intracranial hemorrhage.[22]

MCAs against TNF-alpha (infliximab and adalimumab) are rarely associated with demyelinating disease. Patients may present with encephalopathy, ataxia, paresthesias, optic neuritis, transverse myelitis, and ascending motor neuropathy. The relationship of demyelination and TNF-alpha inhibitors is unclear; however, a temporal relationship is noted between MCA and symptoms. Additional support for a causal relationship is that discontinuation of the drug usually results in resolution of symptoms. Therefore, it is reasonable to avoid these agents in patients with a known personal or family history of demyelinating diseases like multiple sclerosis.

Conclusion

Monoclonal antibodies represent an important and growing category of targeted therapeutic agents. Despite the promise of improved side effect profiles of MCA targeted therapies compared to relatively indiscriminate anti-neoplastic or anti-inflammatory agents serious side effects may still occur. Clinicians will be

seeing increasing numbers of patients on MCAs and should be aware of the diverse spectrum of side effects

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References

1. Common Terminology Criteria for Adverse Events found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
2. Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. *Oncologist* 2008;13:725-32.
3. Vogel WH. Infusion reactions:diagnosis, assessment, and management. *Clin J Oncol Nurs.* 2010;14:E10-21.
4. Centers for Disease Control and Prevention. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha-California, 2002-2003. *MMWR*. 2004;53:683-6.
5. Carson KR, Evens AM, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood*. 2009;113:4834-40.
6. Yousry TA, Major EO, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2006;354:924-33.
7. Clifford DB, De Luca A, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. 2010;9:438-46.
8. Lima MA, Drislane FW, Korainik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurology*. 2006;66:262-4.
9. Post MJ, Yiannoutsos C, et al. Progressive multifocal leukoencephalopathy in AIDS: are there any MR findings useful to patient management and predictive of survical? AIDS Clinical Trials Group, 243 Team. *Am J Neuroradiol*. 1999;20:1896-906.
10. Bongartz T, Sutton AJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295:2275-85.
11. Wallis RS, Broder MS, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis*. 2004;38:1261-5.
12. FDA Requires Stronger Fungal Infection Warning for TNF Blockers found at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107878.htm.
13. Rodriguez M, Fishman JA. Prevention of infection due to Pneumocystis spp. In human immunodeficiency virus-negative immunocompromised patients. *Clin Microbiol Rev*. 2004;17:770-82.
14. Hibberd PL, Tolkoff-Rubin NE, et al. Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. *Ann Intern Med*. 1995;123:18-26.
15. Birzan M, Anselmo M, Carpineta L. Rituximab (B-cell depleting antibody) associated lung injury (RALI): a pediatric case and systemic review of the literature. *Pediatr Pulmonol*. 2009;44:922-34.
16. Liu X, Hong XN, et al. Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hogkin lymphoma. *Leuk Lymphoma*. 2008;49:1778-83.
17. Tokuda Y, Suzuki Y, et al. The role of trastuzumab in the management of HER2-positive metastatic breast cancer: an updated review. *Breast Cancer*. 2009;16:295-300.
18. Jean GW, Shah SR. Epidermal growth factor receptor monoclonal antibodies for the treatment of metastatic colorectal cancer. *Pharmacotherapy*. 2008;28:742-54.
19. Geborek P, Bladstrom A, et al. Tumour necrosis factor blockers do not increase increase overall rumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis*. 2005;65:699-703.
20. Information for Healthcare Professionals about Alemtuzumab found at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125216.htm.
21. Nalluri SR, Chu D, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis *JAMA*. 2008;300:2277-85.
22. Novak JC, Lovett-Racke AE, Racke MK. Monoclonal antibody therapies and neurologic disorders. *Arch Neurol*. 2008;65(9):1162-5.

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Karl Meisel, MD, is a resident at the Rhode Island Hospital Multiple Sclerosis Center.

Syed Rizvi, MD, is an Associate Professor of Neurology and Director of the Rhode Island Hospital Multiple Sclerosis Center.

Correspondence

Syed A. Rizvi, MD
e-mail: SRizvi@Lifespan.org

Monoclonal Antibodies in Rheumatic Diseases

Candice Yuvienco, MD, and Stuart Schwartz, MD

An increased understanding of the immunopathogenesis of rheumatic diseases has dramatically improved the identification of therapeutic targets within the inflammation cascade. These targets include cytokines, B cells, and molecules involved in T cell interactions, which have been pivotal in the initiation and perpetuation of the immune response. Disordered regulation of cytokines, particularly **tumor necrosis factor-alpha (TNF-alpha)**, **interleukin 1 (IL-1)**, and **interleukin-6 (IL-6)** has been well-recognized in inflammatory disorders.[1] Successful isolation of these molecules through advances in biotechnology has led to effective therapies, thus revolutionizing treatment of diseases such as **rheumatoid arthritis (RA)**, **psoriatic arthritis (PSA)**, **ankylosing spondylitis (AS)**, **autoinflammatory syndromes, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)**, and **systemic lupus erythematosus (SLE)**.

Monoclonal antibodies are among these targeted biologic therapies, of which there are now eight in established clinical use for rheumatic disease indications (Table 1): infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), golimumab (Simponi®), tocilizumab (Actemra®), rituximab (Rituxan®), canakinumab (Ilaris®), and recently approved in 2011, belimumab (Benlysta®).[2-27]

Pivotal trials of TNF-inhibitors (infliximab, adalimumab, certolizumab, and golimumab) have proven efficacious in early and longstanding RA, with clinical improvement based on **American College of Rheumatology (ACR)** response criteria. Improvement in functional outcomes, quality of life, and inhibition of radiographic structural damage has been demonstrated. Infliximab, adalimumab, and golimumab have also established efficacy for PSA and AS.

Conventional **disease-modifying anti-rheumatic drug (DMARD)** therapy remains the cornerstone of treatment for RA, particularly **methotrexate (MTX)**. In clinical trials directly comparing MTX with biologics, both were similarly effective. However, improvement began earlier with biologic treatment than with MTX therapy. Inhibition of radiographic progression was more robust with biologics, a finding believed to occur because TNF-inhibitors directly reduce osteoclast activity.[28] Combination therapy with MTX and TNF-inhibitors has consistently proven superior to either given as monotherapy.[2,3,8,9,14]

There are no head-to-head comparison trials of TNF-inhibitors to support the use of one agent over another based on efficacy; they have all been proven effective. Nevertheless, differences in route of administration and dosing intervals may influence the choice of agent. Switching among TNF-inhibitors to overcome inadequate response or poor tolerability appears beneficial in some patients.[29] However, not all patients with RA respond to or tolerate TNF-inhibitors. Additional agents have subsequently emerged which target different cytokines or cells (tocilizumab for IL-6, or rituximab for B cells respectively), offering alternative treatment options for difficult to control cases.

Emerging Clinical Use

Newer applications for existing monoclonal antibodies have evolved. Rituximab, originally indicated for the treatment of lymphoma, was found in the RAVE trial not to be inferior to daily cyclophosphamide treatment to induce remission in severe ANCA-associated vasculitis and may be superior in relapsing disease.[30] The **cryopyrin-associated periodic syndromes (CAPS)**, particularly Muckle Wells and Familial Cold Autoinflammatory Syndrome, typically manifest in the pediatric population but occasionally present in adults. These syndromes have clinical manifestations which include: urticarial-like rash, fever, central nervous system inflammation, arthropathy, and amyloidosis. These syndromes respond dramatically to canakinumab, an anti-IL-1 biologic agent.[25]

Belimumab has been recently approved by the FDA as the first new therapeutic agent for SLE in more than 50 years.

Mechanism of Action

Cytokine-directed therapies:

TNFα plays a central role in the pathogenesis of RA and other inflammatory disorders, mediating both inflammation and articular damage.[1] It is produced primarily by monocytes, macrophages, and B cells, and is inhibited by the monoclonal antibodies infliximab, adalimumab, golimumab, and certolizumab. Blocking TNFα reproducibly inhibited production of other proinflammatory cytokines such as IL-1 and IL-6, confirming that TNFα functions early on in the inflammatory cascade. Furthermore, its blockade reduced leukocyte recruitment to the inflamed joints[1]. Certolizumab has a **PEG (polyethylene glycol)** moiety that prolongs its half-life, which may contribute to preferential distribution to inflamed tissues.[11]

Interleukin-6 is overexpressed in synovial tissue in RA joints, and is a major inducer of the acute phase response. IL-6 activates intracellular signaling that ultimately leads to chronic synovial inflammation. Tocilizumab inhibits IL-6 by competitively binding to its receptor.[19] In CAPS, a cryopyrin mutation leads to the overproduction of the inflammasome, a multiprotein complex that produces IL-1beta. Canakinumab inhibits IL-1beta thereby preventing these autoinflammatory syndromes.[25]

B-cell directed therapies:

RA has a complex pathophysiology in part mediated by self-perpetuating B cell clones, a population of cells that may explain disease persistence. In ANCA associated vasculitis, the number of activated peripheral blood B lymphocytes correlates with disease activity.[30] Rituximab is directed against the CD20 antigen on the B cell membrane causing B cell depletion. This results in a decline of autoantibodies such as rheumatoid factor and anti-cyclic citrullinated peptide in RA, and ANCA in vasculitis.[30,31] Rituximab suppresses the immune response since B cells are no longer available to present antigen to T cells or produce pro-inflammatory molecules.

Belimumab neutralizes **B lymphocyte stimulator (BlyS)**, a potent B cell survival factor. SLE patients have elevated BlyS levels which correlate with their autoantibody titers and disease activity. Inhibition of this factor results in apoptosis of autoreactive B cells.[32,33]

Table 1. Description of the monoclonal antibodies, their indications, mechanism of action, dosing, and corresponding pivotal trials

DRUG (year approved by US FDA)	FDA-approved rheumatic disease indication	Description	Mechanism of action	Usual dose range, route and frequency of administration	Pivotal Trials
infliximab Remicade® (1998)	RA[a], PSA[b], AS[b]	Chimeric	Inhibits TNFα	3-10 mg/kg IV infusion every 8 weeks after initial loading 5 mg/kg used for PSA, AS	ATTRACT[2], ASPIRE[3], IMPACT 1[4] IMPACT 2[5], Braun[6]
adalimumab Humira® (2002)	RA[a,b], PSA[b], AS[b]	Human	Inhibits TNFα	40 mg SC every other week, can increase to weekly	Van De Putte[7], ARMADA[8], PREMIER[9], ATLAS[10]
certolizumab Cimzia® (2008)	RA[a,b]	PEG-linked humanized Fab	Inhibits TNFα	200 SC mg every 2 weeks or 400 mg every 4 weeks after initial loading	RAPID 1[11], RAPID 2[12], FAST4WARD[13]
golimumab Simponi® (2009)	RA[a], PSA[b], AS	Human	Inhibits TNFα	50 mg SC once monthly	GOBEFORE[14], GOFORWARD[15], GOAFTER[16], GOREVEAL[17], GORAISE[18]
tocilizumab Actemra® (2010)	RA[a,b,c]	Humanized	Inhibits IL-6	4-8 mg/kg IV infusion every 4 weeks	OPTION[19], TOWARD[20], RADIATE[21], AMBITION[22]
rituximab Rituxan® (2006)	RA[a,c]	Chimeric	Depletes B cells	1000 mg IV infusion repeated 2 weeks later, then every 24 weeks[d,e]	DANCER[23] REFLEX[24]
canakinumab Ilaris® (2009)	CAPS	Human	Inhibits IL-1	150 mg SC every 8 weeks (adults and children ≥4 years old, >40 kg)	Lachmann[25]
belimumab Benlysta® (2011)	SLE	Human	Inhibits BLYS	10 mg/kg every 2 weeks x 3, then every 4 weeks	BLISS 52[26], BLISS 76[27]

[a] for moderate to severe RA in combination with methotrexate, [b] can be used as monotherapy, [c] for patients with inadequate response to one or more TNF-inhibitor/s, [d] premedicate prior to each infusion with glucocorticoid, antihistamine, and acetaminophen, [e] dose recommendation for RA, with dosing interval based on clinical response

Abbreviations: FDA: Food and Drug Administration; RA: rheumatoid arthritis; PSA: psoriatic arthritis; AS: ankylosing spondylitis; CAPS: cryopyrin-associated periodic syndromes; SLE: systemic lupus erythematosus; PEG: polyethylene glycol; Fab: antigen-binding region of antibody; TNFα: tumor necrosis factor-alpha; IL-1: inerleukin-1; BLYS: B lymphocyte stimulator; IV: intravenous; SC: subcutaneous; mg: milligrams; kg: kilograms.

Safety and Risks

TNFα plays a key role not only in the pathogenesis of inflammatory diseases but also in normal immune homeostasis, host defense, and tumor growth control. As a result, there has been guarded optimism as to the long-term safety of TNF-inhibitors. Clinical trials uncovered the most common adverse events among thousands of patients, and determined that TNF-inhibitors are generally well tolerated. RA itself is associated with an increased risk of infection, lymphoma, and CHF, complicating assessments of these adverse events while on biologic therapy or other immunosuppressants.[29] Safety concerns with the use of TNF-inhibitors are summarized in Table 2, and for non-TNF-inhibitors in Table 3.

General Advisory on the Use of TNF Inhibitors

Decisions to use TNF-inhibitors should always be made on an individual basis, including consideration of all comorbidities, and with clear discussion of the risks and benefits.

Patient and physician vigilance with monitoring for infection is essential,

Table 2. Safety concerns with the use of TNF inhibitors

Serious infections (requiring intravenous antibiotics and/or hospitalization)	Serious, sometimes fatal infections from bacterial, mycobacterial, fungal, viral, or other opportunistic pathogens have been reported.[34-37]
Tuberculosis (TB)	Cases of reactivation or new TB infection have been observed, both pulmonary and disseminated forms. Majority of cases were in countries with high TB incidence rate. TB activation is likely a class effect of TNF inhibitors.[29,34-37]
Opportunistic infections	Histoplasmosis, coccidioidomycosis, aspergillosis, candidiasis, listeriosis, some of these were disseminated, often while on concomitant immunosuppressants.[34-37]
Hepatitis B virus (HBV) reactivation	In chronic carriers, cases of HBV reactivation were seen, the majority in patients who received concomitant immunosuppresants.[34-37]
Demyelinating disease	Rare cases of new-onset/exacerbations of demyelinating disorders of the central (multiple sclerosis, optic neuritis) or peripheral nervous system (Guillain-Barre syndrome) have occurred. Some were temporally related to TNF-inhibitor therapy.[29,34-37]
Immunogenicity	All TNF-inhibitors are foreign proteins that may induce formation of antibodies which may affect safety and efficacy. Antibodies can neutralize the action of these drugs and may cause hypersensitivity reactions. Lower drug doses are more immunogenic than higher doses; chimeric agents (mouse-human structure) are more immunogenic than human monoclonal antibodies; use of concomitant immunosuppressive treatment such as MTX may reduce the magnitude of the immunogenic response.[29,34]
Congestive heart failure	New-onset/worsening of existing heart failure were observed, likely to be a class effect of TNF inhibitors; conflicting data suggested that treatment with TNF inhibitors is associated with decreased prevalence of CHF.[29]
Lupus-like syndrome	Antinuclear and anti-DNA antibody formation have occurred, as well as rare cases of lupus-like syndrome. Most cases were promptly reversible upon withdrawal of medication.[29]
Neoplasia, lymphoma	There have been several reports of lymphoma.[29,34-37] Confounding this relationship is the independently increased risk of lymphoma in advanced/more severe RA.[29] In some trials, there were more cases of malignancy seen in those who received TNF inhibitors versus the control groups.[34,35]
Infusion/injection site reactions	These may be consequences of antibody formation to the drug.[29,34] Patients who developed antibodies to infliximab were more likely to have infusion reactions, the majority of which were mild.[34] Injection site reactions were most commonly erythema, pain, and swelling.
Hematologic events	Postmarketing reports revealed pancytopenia, leukopenia, neutropenia, aplastic anemia, thrombocytopenia.[34-37]
Hepatotoxicity	Severe hepatic reactions were seen, including acute liver failure reports. Elevated transaminases have occurred, however many patients were also on potentially hepatotoxic medications such as methotrexate.[34,36]

with decisions on discontinuation and re-initiation closely reevaluated.

Avoid live vaccines.[29,34-39]

Closely monitor concomitant immunosuppressive/DMARD treatment to limit adverse effects such as hepatotoxicity or hematologic toxicity.[29]

Screening for latent TB by purified protein derivative (PPD) placement is essential, and appropriate treatment should be given accordingly prior to initiation of TNF-inhibitors. If active TB is present, TNF-inhibitor therapy should be delayed until treatment is complete.[29] Monitor all patients for active TB during treatment even if initial PPD is negative, as de novo TB cases have occurred.[29]

Patients at risk for Hepatitis B infection should be screened prior to initiation of TNF-inhibitors. Those with evidence of prior infection should have close monitoring for clinical and laboratory signs of reactivation throughout and after discontinuation of therapy.[29,34-37]

Table 4 summarizes the absolute contraindications to and precautions with the use of TNF-inhibitors. Similar vigilance and precautions should be undertaken with use of the non-TNF-inhibitor monoclonal antibodies (rituximab, tocilizumab, canakinumab, belimumab), particularly with regard to infections, malignancy, demyelinating disorders, pregnancy. Avoidance of live vaccines is emphasized.

Conclusion

The last decade has witnessed the dynamic growth of an effective therapeutic arsenal for a number of chronic inflammatory disorders. Monoclonal antibodies now play an important role in treating rheumatic disease offering significant improvement in clinical, functional, and radiographic outcomes.

Table 3. Safety concerns of non-TNF inhibitor monoclonal antibodies

TOCILIZUMAB	• The most common adverse event was infections, including skin and subcutaneous infections.[21,22] Serious and opportunistic infections have occurred.[19,20,21,22,38]
	• Gastrointestinal perforations complicating diverticulitis, reversible neutropenia and thrombocytopenia, and infusion reactions were seen.[21,38]
	• Aminotransferase elevations, elevations in total cholesterol and low-density lipoprotein levels were reported, however there were no symptoms of hepatitis or cardiovascular events.[21,22]
RITUXIMAB	• Infusion reactions were common adverse events, especially after the first infusion; use of IV steroid prior to infusion reduced these reactions.[23,24,39]
	• Most infections reported in RA patients were mild to moderate, and largely upper respiratory or urinary tract infections.[23,24]
	• There was a slight increase in serious infections compared to placebo in the REFLEX trial (5.2 for rituximab versus 3.7 for placebo per 100 patient-years).[24]
	• Immunogenicity with development of human anti-chimeric antibodies has occurred, but was not associated with increased infusion reactions.[39]
	• Rare cases of progressive multifocal leukoencephalopathy cases have been reported.[39]
CANAKINUMAB	• There were no reported deaths or life-threatening adverse events.[25]
	• Vertigo was reported in a small percentage, and 34% developed infections.[25]
	• There were no cases of malignancy, opportunistic infections, autoantibodies to canakinumab, autoimmune or demyelinating adverse events.[25]
BELIMUMAB	• Overall adverse events in studies of belimumab in SLE patients demonstrated that rates of serious infections were comparable across treatment groups, and rate of opportunistic infections were stable over time.[40]
	• Malignancies were seen, however no pattern or increase in any particular type of malignancy was identified in the belimumab group.[40]

Table 4. Absolute contraindications and precautions with use of anti-TNF therapy

ABSOLUTE CONTRAINDICATIONS	PRECAUTIONS
Active, latent, untreated tuberculosis	Chronic or recurrent infection
Active serious infection/sepsis	Hepatitis C, hepatitis B infection/ carrier
Active or recent history of malignancy other than successfully treated non-melanoma skin cancer	Malignancy in remission
Demyelinating disease	Human immunodeficiency virus infection
Live vaccines	Pregnancy
Lymphoma	Lactation
Known anaphylaxis to product	Systemic lupus erythematosus
Combination with anakinra or abatacept, which increases risk of infection without increase in benefit	Lupus-like syndrome
CHF class III/IV	CHF class I/II

TNF: tumor necrosis factor; CHF: congestive heart failure
Modified from: Hochberg MC, Lebwohl MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. *Semin Arthritis Rheum*. 2005 Jun;34(6):819-36.

TNF inbibitors have become the first line treatment in rheumatoid arthritis for methotrexate failures. Rituximab and tocilizumab are presently reserved for TNF failures. Despite their significant expense and unique safety profile, monoclonal antibodies have dramatically improved the management of several rheumatic diseases.

References

1. Andreakos ET, Foxwell BM, et al. Cytokines and anti-cytokine biologicals in autoimmunity: present and future. *Cytokine Growth Factor Rev*. 2002 Aug-Oct;13(4-5):299-313.
2. Lipsky PE, Van Der Heijde DM, et al: Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med*. 2000; 343:1594-1602.
3. St Clair EW, Van Der Heijde DM, et al: Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum*. 2004; 50:3432-3443.
4. Antoni C, Kavanaugh, et al: Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum*. 2005; 52:1227-1236.
5. Kavanaugh A, Krueger G, et al: Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis*. 2007; 66:498-505.
6. Braun J, Brandt J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet*. 2002 Apr 6;359(9313):1187-93.
7. Van De Putte LB, Atkins C, et al: Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom

previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis*. 2004; 63:508-516.
8. Weinblatt ME, Keystone EC, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003 Jan;48(1):35-45.
9. Breedveld FC, Weisman MH, et al: The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum*. 2006; 54:26-37.
10. Van der Heijde D, Kivitz A, et al, ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2006 Jul;54(7):2136-46.
11. Keystone E, Heijde D, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum*. 2008 Nov;58(11):3319-29.
12. Smolen J, Landewé RB, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis*. 2009 Jun;68(6):797-804.
13. Fleischmann R, Vencovsky J, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis*. 2009 Jun;68(6):805-11. Epub 2008 Nov 17.
14. Emery P, Fleischmann RM, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum*. 2009 Aug;60(8):2272-83.
15. Keystone EC, Genovese MC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis*. 2009 Jun;68(6):789-96. Epub 2008 Dec 9.
16. Smolen JS, Kay J, et al, GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet*. 2009 Jul 18;374(9685):210-21. Epub 2009 Jun 26.
17. Kavanaugh A, McInnes I, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum*. 2009 Apr;60(4):976-86.
18. Inman RD, Davis JC Jr, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum*. 2008 Nov;58(11):3402-12.
19. Smolen JS, Beaulieu, A et al; OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet*. 2008 Mar 22;371(9617):987-97.
20. Genovese MC, McKay JD, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum*. 2008 Oct;58(10):2968-80.
21. Emery P, Keystone E, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis*. 2008 Nov;67(11):1516-23. Epub 2008 Jul 14.
22. Jones G, Sebba A, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis*. 2010 Jan;69(1):88-96.
23. Emery P, Fleischmann R, et al; DANCER Study Group. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum*. 2006 May;54(5):1390-400.
24. Cohen SB, Emery P, et al; REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*. 2006 Sep;54(9):2793-806.
25. Lachmann HJ, Kone-Paut I, et al; Canakinumab in CAPS Study Group. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med*. 2009 Jun 4;360(23):2416-25.
26. Navarra S, Thomas M, et al. Belimumab, a BlyS-specific inhibitor reduced disease activity, flares and steroid use in patients with seropositive systemic lupus erythematosus (SLE): BLISS-52 study. *Int J Rheum Dis*. 2010; 13 (Suppl. 1):110-115. Abstract 0282, NCT00424476.
27. Furie RA, Gladman D, et al, Belimumab : A BLyS specific inhibitor, reduced disease activity and severe flares with seropositive SLE: BLISS-76 study. *Lupus*. 2010, 19S:13.
28. Rau R. Efficacy of methotrexate in comparison to biologics in rheumatoid arthritis. *Clin Exp Rheumatol*. 2010 Sep-Oct;28(5 Suppl 61):S58-64. Epub 2010 Oct 28.
29. Hochberg MC, Lebwohl MG, et al. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. *Semin Arthritis Rheum*. 2005 Jun;34(6):819-36.
30. Stone JH, Merkel PA, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010 Jul 15;363(3):221-32.
31. Cohen B. Targeting the B cell in Rheumatoid Arthritis. *Best Practice & Research Clinical Rheumatology*. 24 (2010): 553-563.
32. Petri M, Stohl W, et al. Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus. *Arthritis Rheum*. 2008; 58:2453–2459.
33. Wallace DJ. Advances in drug therapy for systemic lupus erythematosus. *BMC Med*. 2010 Nov 29;8(1):77. [Epub ahead of print]
34. Centocor Ortho Biotech Inc. Remicade (infliximab) [package insert] Malvern, PA 2010.
35. Abbott Laboratories. Humira (adalimumab) [package insert] North Chicago, IL 2009.
36. UCB. Cimzia (certolizumab) [package insert] Smyrna, GA 2009.
37. Centocor Ortho Biotech Inc. Simponi (golimumab) [package insert] Horsham, PA 2010.
38. Genentech, Inc. Actemra (tocilizumab) [package insert] South San Francisco, CA 2010.
39. Biogen Idec Inc. and Genentech, Inc. Rituxan (rituximab) [package insert] South San Francisco, CA 2010.
40. Wallace D, Navarra S, et al. Safety Profile of Belimumab, a BLys-Specific Inhibitor, in Patients With Active Systemic Lupus Erythematosus (SLE): Pooled Data From Phase 2 and 3 Studies. Poster presented at American College of Rheumatology 2010 Annual Meeting; November 7-11, 2010; Atlanta, GA.

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Candice Yuvienco, MD, is a fellow of Rheumatology at Rhode Island Hospital.

Stuart Schwartz, MD, is a Clinical Associate Professor of Medicine at the Warren Alpter Medical School of Brown University.

Correspondence

Stuart Schwartz, MD
2 Dudley St., Suite 370
Providence, RI 02905
e-mail: SSchwartz@Lifespan.org

Use of Monoclonal Antibodies in Oncology

Humera Khurshid, MD, and Natalie Sinclair, MD

Monoclonal antibodies (MCA) represent a significant addition to therapeutic options for a number of oncologic disorders. MCA are highly specific. They bind to and affect disease specific targets resulting in sparing of normal cells with less side effects than traditional chemotherapy. This review focuses on MCA approved for clinical use.

MCA are produced by a single clone of B cells and are mono specific. These antibodies can block essential cellular receptors, directly induce apoptosis, bind to target cells, and recruit antibody-dependant cellular or complement-dependent cytotoxicity mechanisms. They can also deliver cytotoxic chemicals such as radioisotopes and toxins. The pharmacologic characteristics are summarized. [Table 1]

The **Food and Drug Administration (FDA)** has approved several MCA for oncologic indications.

Rituximab

Rituximab was the first approved MCA. This chimeric IgG molecule binds with high specificity to the CD20 molecule on lymphoid cells of B lineage. Rituximab is active against CD20 positive **Non Hodgkins Lymphoma (NHL)**.

Low Grade Non Hodgkins Lymphomas

In a pivotal phase II trial, heavily pretreated patients with relapsed low grade NHL were given single agent rituximab intravenously weekly for four weeks. Forty eight percent of patients responded with a median response of 12 months.[1] After retreatment the response rate was around 40%.[2] Rituximab was found to be effective and safe when combined with standard first line chemotherapy. In the phase III trial involving CD20 positive follicular NHL patients the response rate was 81% in the combination group (**Cyclophosphamide, Vincristine and Prednisone (CVP)**

Table 1.

Monoclonal Antibody	Target	Mechanism	Indication	US FDA Approval Date	Adverse Reaction
Rituximab (Rituxan)	CD 20	ADCC, CDC, Directly induces apoptosis	NHL Maintenance in NHL	11/26/1997 1/28/201	Allergic Reactions Tumor Lysis Syndrome
Trastuzumab (Herceptin)	HER 2	Inhibition of HER2-mediated tumor cell proliferation and migration	Breast Cancer	9/25/1998	Cardiac complications Allergic reactions
Cetuximab (Erbitux)	EGFR	Inhibits EFGR mediated tumors cell invasion, proliferation metastatis, Enhances Activity of some chemotherapuetic and radiotherapy	Colon Head and neck cancer	2/12/2004 3/1/2006	Allergic reactions and skin rash
Penitumumab (Vectibix)	EGFR	Inhibits EFGR mediated tumors cell invasion, proliferation metastatis,	Colon	9/27/2006	Dermatologic toxicity
Bevacizumab (Avastin)	VEGF	Inhibiton of VEGF induced angiogenesis	Metastatic Non squamous lung Colon Met Renal cell ca Recurrent gliomas Met Breast	10/11/2006 2/26/2004 7/31/2009 5/5/2009 12/16/2010	Proteinuria Hypertension Thrombosis Reduced wound healing Pulmonary Hemorrhage in squamous histology
Alemtuzumab (Campath)	CD 52	ADCC, CDC	CLL	5/7/2001	Pancytopenia, Lymphopenia

with Rituximab) vs. 57 % in patients given CVP alone [P = < 0.001]. Time to treatment failure was longer in the combination group 27 vs. seven months [P = < 0.001]. Benefit was not associated with any significant increase in toxicity.[3]

In January 2011 the US FDA approved Rituximab for maintenance therapy for previously untreated CD20 + B cell NHL that achieved a response. This was based on the **PRIMA study** (**Primary Rituximab and Maintenance Phase III intergroup trial**). After achieving a response to systemic chemotherapy, 1018 patients were randomized in a 1:1 manner to receive either rituximab 375 mg/m2, intravenously every eight weeks with a maximum of 12 doses vs. observation. **Progression free survival** (**PFS**) was the primary endpoint and treatment. Rituximab increased PFS by 46 % [P = < 0.001]. A higher percent of patients had a complete response at 2-4 months with Rituximab maintenance [67 vs. 48 %].[4]

High Grade Non-Hodgkins Lymphoma

In a randomized phase III study of **Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone** (**CHOP**) chemotherapy with or without rituximab in treatment naive patients, the rituximab arm showed a higher PFS, (53 vs. 35 % P = 0.0008) without increased toxicity.[5,6] A phase III study, the MabThera International Trial (or MInT trial), enrolled patients with high grade lymphoma, aged 18-60 years and compared CHOP plus rituximab with chemotherapy alone as first line treatment . The study was closed early when interim analysis showed a significantly longer time to treatment failure in the combination group. After a follow up of 34 months patients assigned to R-CHOP had significantly higher PFS, (79% vs. 59%) and overall survival OS, [93% vs. 84%].[7]

Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia

Rituximab is also active in **Chronic Lymphocytic Leukemia** (**CLL**).[8] In a phase II study by the Cancer and Leukemia Group B, fludarabine plus Rituximab based therapy in previously untreated patients gave a higher response rate and complete remission than chemotherapy alone.[9]

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that targets HER2 also known as C-erb-B2, a member of the EGFR family. HER2 is over expressed in about 25-30% of breast cancer. Over expression in early stage breast cancer is associated with poor prognostic factor such as high tumor grade,[10] axillary lymph node involvement,[11] increase mitotic rate,[12] and lack of estrogen and progesterone receptor expression.[13] It is also an independent adverse prognostic factor.[14]

In a phase III trial patients with **metastatic breast cancer** (**MBC**) with HER2 over expression, untreated patients were randomized to receive standard chemotherapy with and without Trastuzumab. Those who received Trastuzumab plus chemotherapy had a longer time to disease progression, 7.4 months vs. 4.6 months [P = < 0.001], a highly objective response rate, 50% vs. 32% [P = < 0.001], a longer median duration of response, 9.1 vs. 6.1 months, [P = < 0.0001], longer median survival, 25.1 months vs. 20.3 months [P = 0.046], and a 20 % lower risk of death than patients who had received chemotherapy alone.[15]

Addition of trastuzumab to adjuvant chemotherapy significantly reduces the likelihood of disease relapse and death among women with HER2 positive early stage breast cancer. Two North American cooperative group trials were designed to evaluate the efficacy of adjuvant trastuzumab. In the **National Surgical Adjuvant Breast and Bowel Project trial** (**NSABP B-31**), 1736 patients with Her2 positive breast cancer received 4 cycles of doxorubicin and cyclophosphamide [AC] followed by four cycles of paclitaxel 175mg/m2 every three weeks. They were randomly assigned to no further therapy or weekly trastuzumab beginning with the first course of paclitaxel. The **North Central Cancer Treatment Group** (**NCCTG trial N9831**) tested the value of adding trastuzumab to sequential AC and paclitaxel in concurrent vs. sequential trastuzumab and paclitaxel. In this trial, 1615 women with HER2 positive lymph node or high risk node negative breast cancer (greater than 1cm ER negative or greater than 2cm ER positive) received AC in one of the three different treatment strategies. Weekly paclitaxel for 12 weeks alone, weekly paclitaxel followed by trastuzumab for 52 weeks, or weekly paclitaxel with concurrent trastuzumab followed by trastuzumab alone for 40 weeks.[16,17] Combined analysis demonstrated that adjuvant trastuzumab paired with paclitaxel chemotherapy resulted in a greater than 50 % reduction in recurrence risk, with a four year disease free survival of 86% vs. 73% and a 37% reduction in risk of death. The four year overall survival was 93% vs. 89%. This led to FDA approval and established adjuvant traztuzumab as the standard of care.[18] Similar results were found in early analysis of a large multinational trial, the **Herceptin Adjuvant study** (**HERA trial**).[19]

Trastuzumab is associated with the risk of cardiotoxicity manifested by an asymptomatic decline in the left ventricle ejection fraction and less commonly development of New York Heart Association Class III or IV.[20] The cardiac toxicity may be reversible in many patients and responds to standard treatments for heart failure. Anthracycline use and age greater than 60 years are the strongest risk factors for development of trastuzumab-related cardiac toxicity.

Cetuximab

Epidermal Growth factor Receptor (**EGFR**) also known as HER-1 is a tyrosine kinase receptor and a member of the EFGR family. Over-expression is seen in various epithelial tumors such as lung, breast, head and neck and colon. Over expression is associated with a poor prognosis.[21-23]

Metastatic Colorectal Cancer (CRC)

Cetuximab is a chimeric monoclonal antibody that binds to EGFR, blocking its binding to its receptor thus preventing receptor activation and downstream signaling. Two monoclonal antibodies that target EFGR are active for treatment of metastatic colorectal cancer, cetuximab and panitumamab. KRAS, the protein product of the Ras oncogene, serves as a mediator between extracellular ligand binding and intracellular transduction signals from EGFR to the nucleus. Activating KRAS mutations are detected in approximately 40% of metastatic colorectal cancer, with good concordance between the primary and distant metastasis.[24] KRAS mutations are associated with poor prognosis and overall resistance to

EGFR therapy. Panitumumab and Cetuximab are approved only for patients with wild type KRAS tumors. KRAS mutation analysis is commercially available.

Cetuximab monotherapy was compared to best supportive care in a randomized trial of 572 heavily pretreated patients with Metastatic CRC.[25] Median OS was significantly better with cetuximab (6.1 vs. 4.6 months), and quality of life measures were also improved in the treatment arm. In a subsequent analysis, the benefit of Cetuximab was restricted to patient who lacked KRAS mutation (wild type KRAS). Cetuximab has also been used with chemotherapy with encouraging results.[26] First line Cetuximab was evaluated in patients with previously untreated metastatic CRC, 1198 were randomized to **5-FU, leucovorin, and irinotecan (FOLFIRI)** with or without Cetuximab.[27] Median PFS was modestly better in patients with combined therapy, 8.9 vs. eight months, as was the overall response rate (47% vs. 39%). However there was no significant difference in OS. In a preliminary report in patients with wild type KRAS, response rates were significantly higher in those who received cetuximab in conjunction with chemotherapy.[28] Cetuximab is indicated only for patients with wild type KRAS tumors.

Panitumumab is fully human monoclonal antibodies specific for the extra cellular domain of EGFR. Panitumumab is approved in the US as a single agent for KRAS wild type metastatic colorectal cancer after other drugs have failed.[29]

Head and neck cancer

Cetuximab was compared concurrently with RT vs. RT alone in a multinational randomized study of patients with locally advanced head and neck carcinoma.[30] Compared to RT alone the addition of cetuximab significantly improved the duration of local control, (24 vs. 15 months), as well as PFS, (42% vs. 39%), and OS (55% vs. 45%). Importantly comparison of RT alone is no longer the accepted standard for patients with locally advanced head and neck cancer. As the toxicity profile of RT and cetuximab is viewed to be more tolerable compared to chemo-radiotherapy, some may consider it to be more of a substitute for chemo-radiotherapy particularly in the treatment of elderly patients. Current data does not support the use of cetuximab in combination with platinum and radiation therapy. Randomized trials are currently underway to evaluate this combination therapy.

Panitumumab is fully human monoclonal antibodies specific for the extra cellular domain of EGFR.

Cetuximab has shown benefit in patients with metastatic squamous cell carcinoma of the head and neck with combined cisplatin based chemotherapy.[31] In a randomized phase III trial involving 442 patients with recurrent or metastatic head and neck squamous cell carcinoma patients assigned to first line platinum chemotherapy with or without cetuximab. The addition of cetuximab to chemotherapy significantly prolonged the median PFS and OS (5.6 and 10.1 month vs. 3.3 and 7.4 months respectively).[32] Common side effects of cetuximab include acneiform rash, hypomagnesemia, fever, and gastrointestinal symptoms.

Bevacizumab

Bevacizumab is a humanized murine monoclonal antibody that targets vascular endothelial **growth factor receptor A (VEGF)**. VEGF is an important cell specific mitogen that regulates vascular proliferation and permeability. It also functions as anti apoptotic factor for newly formed blood vessels. (33). The antibody targets the process of angiogenesis and the acquisition of new blood vessels by the tumor.

Colorectal cancer

Addition of bevacizumab to a variety of first line regimens used for metastatic colorectal cancer improves outcome. In a randomized phase II trial previously untreated patients were assigned to **bolus irinotecan, fluorouracil (IFL)** with or without bevacizumab. Response rates were higher with bevacizumab and it prolonged median survival by 4 months.[34] Similar results were seen in a phase III trials of bevacizumab in combination with **FOLFOX (5-FU, Leucovorin, and Oxaliplatin)** for first line treatment in metastatic CRC[35] Bevacizumab is active in first line metastatic CRC in combination with oxaliplatin and irinotecan based regimens.[36]

Non squamous non small cell lung cancer (NSCLC)

The initial phase II study investigating a combination of paclitaxel and carboplatin with or without bevacizumab raised safety concerns. Patients with squamous cell histology had higher incidences of fatal pulmonary hemorrhage (~30%). Other risk factors were cavitary lesions, hemoptysis, and brain metastases.[37]

A pivotal phase III trial conducted by **Eastern Cooperative Oncology Group (ECOG 4599)** included 878 previously untreated NSCLC. They were randomized to carboplatin and paclitaxel given every 21 days for six cycles vs. the same doublet combination with bevacizumab. Patients with squamous cell carcinoma, hemoptysis, or history of brain metastases were excluded to minimize the risk of pulmonary or intracerebral hemorrhage. Patients receiving chemotherapy plus bevacizumab had a significant increase in the objective response rate, (35% vs. 15%,) with an overall survival of 12.3 months vs. 10.3 month. One year and two years survival were 51% vs. 44% and 53% vs. 50% respectively.[38] The bevacizumab containing regimen was generally well tolerated. In a second trial conducted in Europe, there was a benefit in terms of PFS however there was no significant difference in OS between treatment arms.[39]

Metastatic Breast Cancer (MBC)

Bevacizumab is FDA approved for breast cancer that does not over express Her2. In the ECOG 2100 trial, 722 women with no prior treatment for MBC were randomly assigned to bevacizumab and paclitaxel or paclitaxel alone.[40] Bevacizumab combined with paclitaxel significantly increased the response rate 37% vs. 21%. and PFS (11.8 months from 5.9 months). In a similar trial the combination of bevacizumab and docetaxel was found to be more beneficial.[41] Pooled analysis from these trials show improvement in PFS but no improvement in OS.

Recurrent Malignant Gliomas (GBM)

Bevacizumab has demonstrated significant clinical activity in phase II single arm studies, both as single agent and when given with irinotecan to patients with grade 3 and grade 4 malignant GBM. The most extensive experience with bevacizumab comes from a randomized non-comparative phase II trial in which 167 patients with recurrent GBM were randomly assigned to bevacizumab either as a single agent or in conjunction with irinotecan.[42] Treatment cycles where repeated every two weeks. All patients received prior chemotherapy with temozolomide. In this trial the objective response rate with bevacizumab alone or with combination with irinotecan was 28% vs.38% respectively and the six month PFS rates and OS were 43% and 53%, 9.2 months and 8.7 months respectively. Treatment with bevacizumab or bevacizumab plus irinotecan was generally well tolerated and toxicity was limited to that expected with these agents.[43]

Metastatic Renal Cell Carcinoma

In a randomized phase II trial single agent bevacizumab improved PFS in patients with advanced renal cell cancer who progressed after immunotherapy.[44]

Two phase III trials have had similar results demonstrating improvement in PFS with the use of bevacizumab plus interferon alpha compared to Interferon alpha alone. [45, 46] Both of these trials excluded patients with brain metastases because of concern for intracranial hemorrhage. The FDA approved avastin for use in combination with Interferon alpha for the treatment of patients with metastatic renal cell carcinoma.

Avastin may have serious side effects including bleeding, thromboses, hypertension, and proteinuria,

Alemtuzumab

Alemtuzumab targets CD-52 and is approved for the treatment of refractory CLL, although it has not been compared with Fludarabine based regimens. Both Alemtuzumab and Fludarabine based therapy have demonstrated superior response rates compared to Chlorambucil based therapy alone. Alemtuzumab alone results in an overall response and complete response rates of approximately 83% and 24% respectively.

In a phase III trial, 297 previously untreated and symptomatic patients with RAI stage I-IV CLL were randomly treated to Alemtuzumab or Chlorambucil.[47] At follow up of 25 months patients treated with alemtuzumab had a higher overall response rate 83% vs. 55% and PFS was 15 month vs. 12 months. On subset analysis higher response rates were seen in high risk patients. The study was not powered to find an OS difference.

Alemtuzumab related toxicity include, lymphopenia, leukopenia, high rate of febrile neutropenia as well as infusion related hypotension, fever, dyspnea, bronchospasm, rash, rarely pulmonary infiltrates, ARDS, and cardiac arrest.

Conclusion

Monoclonal antibodies have been among the most important additions to the therapeutic portfolio of malignant disorders. In most circumstances the effect seems greatest when combined with cytotoxic agents. Several questions remain unanswered including the role of these agents both in mono and combined therapy, duration of use, and the challenge of limiting toxicity. Ongoing and future clinical trials will help define the role of these agents in the treatment of cancer.

References

1. McLaughlin P, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16(8):2825-33.
2. Davis TA, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. *J Clin Oncol*. 2000;18(17):3135-43.
3. Marcus R, et al. An international Multi-Centre, Radomized, Open Label, Phase III Trial Comparing Rituximab Added to CVP Chemotherapy to CVP Chemotherapy Alone in Untreated to Non-Hodgkins Lymphoma. *Blood*. 2003;102(11):Abtract 87.
4. Salles G, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 377(9759):42-51.
5. Coiffier B, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4):235-42.
6. Coiffier B, Tilly H, Herbrecht R, GELA study comparing CHOP and R-CHOP in elderly patients with DLCL: 3 year median follow up with an analysis according to co-morbidity factors. *J Clin Oncol*. 2003;21:abtsract 2395.
7. Pfreundschuh M, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7(5):379-91.
8. Hainsworth JD, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol*. 2003;21(9):1746-51.
9. Byrd JC, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). *Blood*. 2003;101(1):6-14.
10. Berger MS, et al. Correlation of c-erbB-2 gene amplification and protein expression in human breast carcinoma with nodal status and nuclear grading. *Cancer Res*. 1988;48(5):1238-43.
11. Slamon DJ, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*. 1989;244(4905):707-12.
12. Borg A, et al. ERBB2 amplification in breast cancer with a high rate of proliferation. *Oncogene*. 1991;6(1):137-43.
13. Quenel N, et al. The prognostic value of c-erbB2 in primary breast carcinomas: a study on 942 cases. *Breast Cancer Res Treat*. 1995;35(3):283-91.
14. Slamon DJ, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783-92.
15. Slamon DJ, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-82.
16. Romond EH, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673-84.
17. Perez E. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. *J Clin Oncol*. 2008;25(18s).
18. Perez EA, et al. ACCO: ASCO core curriculum outline. *J Clin Oncol*. 2005;23(9):2049-77.
19. Smith I, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007;369(9555):29-36.
20. Ewer SM, Ewer MS, Cardiotoxicity profile of trastuzumab. *Drug Saf*. 2008;31(6):459-67.
21. Salomon DS, et al. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol*. 1995;19(3):183-232.
22. Kim ES, Khuri FR, Herbst RS. Epidermal growth factor receptor biology (IMC-C225). *Curr Opin Oncol*. 2001;13(6):506-13.
23. Porebska I, Harlozinska A, Bojarowski T. Expression of the tyrosine kinase activity growth factor receptors (EGFR, ERB B2, ERB B3) in colorectal adenocarcinomas and adenomas. *Tumour Biol*. 2000;21(2):105-15.
24. Santini D, et al. High concordance of KRAS status between primary colorectal tumors and related metastatic sites: implications for clinical practice. *Oncologist*. 2008;13(12):1270-5.

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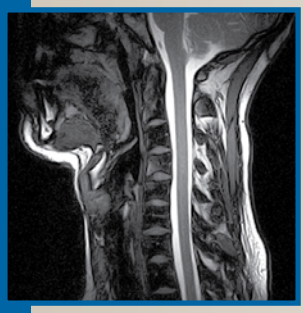

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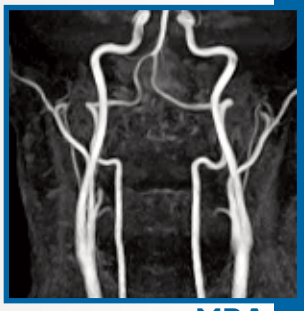

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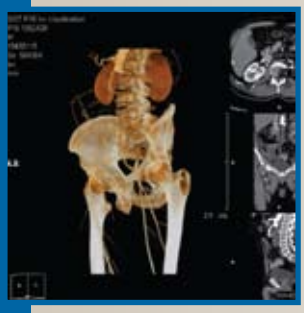

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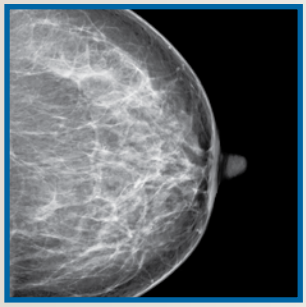

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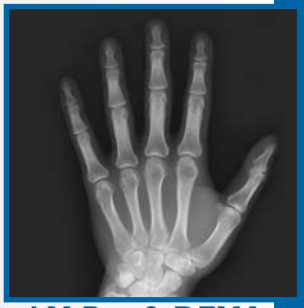

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25. Jonker DJ, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007;357(20):2040-8.
26. Sobrero AF, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26(14):2311-9.
27. Van Cutsem E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360(14):1408-17.
28. Van Cutsem E, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol*. 2009;20(11):1842-7.
29. Hecht JR, et al. Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. *Cancer*. 2007;110(5):980-8.
30. Bonner JA, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354(6):567-78.
31. Burtness B, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol*. 2005;23(34):8646-54.
32. Vermorken, JB, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359(11):1116-27.
33. Rosen LS. Clinical experience with angiogenesis signaling inhibitors: focus on vascular endothelial growth factor (VEGF) blockers. *Cancer Control*. 2002;9(2 Suppl):36-44.
34. Hurwitz H, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-42.
35. Hochster HS, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol*. 2008;26(21):3523-9.
36. VanCutsem E. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Annals of Oncology*. 2009:1882-5.
37. Johnson DH, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184-91.
38. Sandler A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-50.
39. Reck M, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol*. 21(9):1804-9.
40. Miller K, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007;357(26):2666-76.
41. Miles DW, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 28(20):3239-47.
42. Friedman HS, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27(28):4733-40.
43. Cloughesy T, et al. Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study. *J Clin Oncol*. 28(15s):Abstract.
44. Yang JC, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med*. 2003;349(5):427-34.
45. Escudier B, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol*. 28(13):2144-50.
46. Rini BI, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol*. 28(13):2137-43.
47. Hillmen P, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2007;25(35):5616-23.

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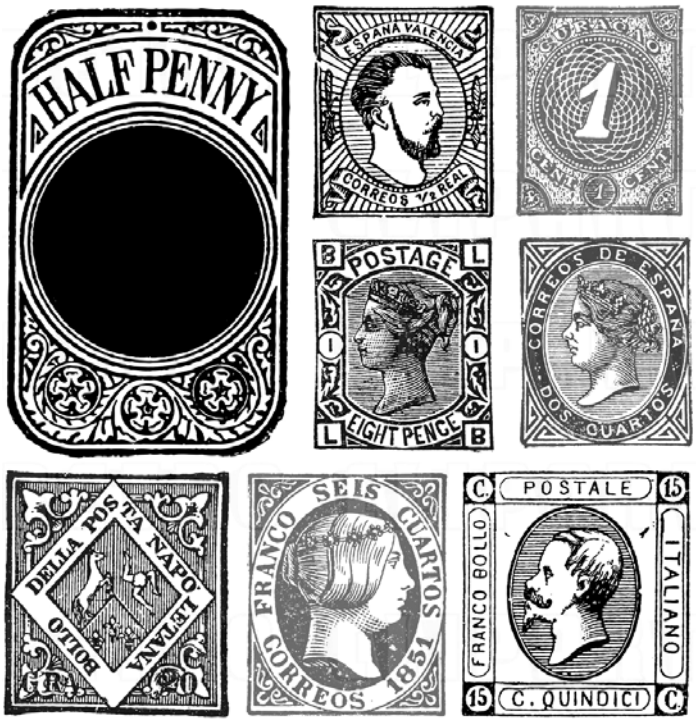
Humera Khurshid, MD, is an Assis tant Professor of Medicine at the Warren Alpert School of Medicine at Brown University, and Oncologist at the Comprehensive Cancer Center at Rhode Island Hospital.

Natalie Sinclaire, MD, is a Heamtology and Oncology Fellow at the Warren Alpert School of Medicine at Brown University.

Correspondence

Humera Khurshid, MD
e-mail: Hkhurshid@lifespan.org



The Role of Monoclonal Antibodies in Neurological Disorders

Valerie Gendron, MD, and Syed A. Rizvi, MD

Monoclonal antibody treatment is standard therapy for multiple sclerosis and is under investigation for neuromyelitis optica, peripheral neuropathies, and inflammatory myopathies. This review will highlight the uses of monoclonal antibodies in these diseases.

Multiple Sclerosis

In multiple sclerosis, autoreactive T cells cross the blood-brain barrier under the influence of proinflammatory cytokines and cellular adhesion molecules, resulting in an attack on myelin, with resulting inflammation, degeneration and demyelination.[1] Given the multitude of interactions involved in the immunopathogenesis of multiple sclerosis, several immunological pathways may be targeted with highly specific and selective antibodies.

Natalizumab

At present time, the only FDA approved monoclonal antibody for the treatment of multiple sclerosis is natalizumab, a humanized monoclonal antibody directed against the α4 subunit of the α4β1 integrin, also known as **very late antigen-4 (VLA4)**, which is expressed on the surface of activated lymphocytes. **Vascular cell adhesion molecule (VCAM)**, expressed on the luminal surface of vascular endothelium, acts as the receptor for VLA4. Their interaction ultimately results in lymphocyte adhesion to vascular endothelium and lymphocyte translocation across the endothelium. By its action on VLA4, natalizumab blocks this interaction, in effect inhibiting lymphocyte migration across the blood brain barrier.[2,3,4,5]

Early studies on natalizumab had shown positive results, which led to two phase III multicenter randomized control studies. The first study, AFFIRM, randomized 942 patients to receive either natalizumab or placebo by intravenous infusion every four weeks. Natalizumab was found to reduce the risk of sustained progression of disability by 42% over two years, reduce the accumulation of new or enlarging hyperintense T2 MRI lesions by 83% over two years, and reduce the rate of clinical relapse by 68% at one year.[6] The second study, SENTINEL, randomized 1171 patients having at least one relapse in 12 months while on beta-1a therapy, to receive either beta-1a plus natalizumab, or beta-1a plus placebo by intravenous infusion every four weeks. Combination therapy with natalizumab was found to reduce the risk of sustained disability progression by 24%, reduce the rate of clinical relapse by 54% at one year and by 55% at two years, and reduce the number of new or enlarging hyperintense T2 lesions by 83% at two years.[7]

Based on promising data at one year outcome measures, and a generally tolerable side effect profile, natalizumab was approved in November 2004, prior to completion of the phase three studies. Three months later, in February 2005, two patients were found to have developed **progressive multifocal leukoencephalopathy (PML)**, both of whom had received combination therapy with beta-1a in the SENTINEL trial. Natalizumab was voluntarily withdrawn from the market. In June 2006, it was placed back on the market, with the caveat that it be used as monotherapy in patients with relapsing forms of MS.[3,4,5]

Natalizumab is currently being used as a second line agent in the treatment of **relapsing and remitting (RRMS)** or **secondary progressive (SPMS)** with relapses with excellent tolerability and encouraging results. The risk of PML remains and seems to increase with duration of therapy. At the time of writing this manuscript more than 90 cases of PML have been reported, with a mortality of about 20%, out of a total of approximately 83,000 patients exposed to natalizumab (press release). There are ongoing studies of the safety of natalizumab continues, through both the **Tysabri Outreach Unified Commitment to Health (TOUCH)** program, requiring enrollment before receiving the drug in the United States, and through the **Tysabri Global Observational Program in Safety for Rest of World (TYGRISROW)**, a safety observational cohort program designed to obtain long-term safety data in MS patients treated outside of the US.[3,4,5]

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a cell surface antigen located on T cells, B cells, monocytes, macrophages, and eosinophils. Its mechanism of action is still unknown, but its end result is profound lymphopenia. Early studies of alemtuzumab showed significantly reduced annual relapse rate in both relapsing-remitting and secondary progressive MS. Despite this, the secondary progressive group showed sustained disability, while the relapsing-remitting group showed a reduction in disability. [8] This was followed by a phase 2 study, including 334 patients with early relapsing-remitting multiple sclerosis randomized to either subcutaneous interferon beta-1a three times per week or annual intravenous alemtuzumab at either 12mg or 24mg over 36 months. Alemtuzumab was found to significantly reduce the rate of disability, the annual relapse rate, and the lesion burden on MRI when compared to interferon beta 1a. Patients receiving alemtuzumab were found to have significantly higher rates of autoimmune disorders, most commonly hyperthyroidism and immune thrombocytopenic purpura. [9] There are currently two phase three trials underway, CARE-MS I, comparing alemtuzumab to interferon beta-1a in treatment naïve patients, and CARE-MS II, comparing alemtuzumab to interferon beta-1a in patients who have received an adequate trial of disease modifying therapy, but continue to have relapses. All patients receiving alemtuzumab in these studies are also followed in an extension study designed to evaluate safety and efficacy.[10]

Daclizumab

Daclizumab is a humanized monoclonal antibody, directed against CD25

surface antigen, which is identical to the interleukin-2 receptor, located on activated T cells. Interleukin-2 induces secretion of proinflammatory cytokines and stimulates proliferation of lymphocytes. Daclizumab acts as an antagonist at the interleukin-2 receptor. Results from preliminary open label trials showed significantly decreased numbers of contrast enhancing lesions on MRI, decreased exacerbation rates, and decreased **Expanded Disability Status Scale (EDSS)** scores. Decreased EDSS scores were also observed in five of 14 patients with secondary progressive multiple sclerosis, an important finding, as there is currently no therapeutic option for this group of patients.[3,4,5,11] A phase II study of nine patients with multiple sclerosis on interferon therapy, with continued relapses and contrast enhancing lesions, showed significant reduction in contrast enhancing lesions, number of relapses, EDSS scores, timed ambulation scores, and neurologic rating scale.[12] A larger, phase II study, CHOICE, included 230 patients already on interferon beta, randomized to combination therapy with daclizumab subcutaneously injected at a dose of either 2mg/kg every two weeks, or 1mg/kg every four weeks versus combination therapy with placebo. There was a statistically significant decrease in the mean number of new or enhancing lesions in the high dose daclizumab group. [13] Phase III trials are currently underway, evaluating daclizumab vs. interferon beta-1a as well as safety and efficacy studies.[10]

Rituximab

Rituximab is a chimeric monoclonal antibody against CD-20 antibodies expressed on B cells. It causes B cell lysis though its effects on complement activation, antibody-dependent cellular cytotoxicity, and apoptosis. A phase II, double blind, trial involving 104 patients with relapsing remitting multiple sclerosis assigned to either rituximab or placebo showed that patients receiving rituximab had significantly fewer total and new gadolinium enhancing lesions on MRI, and fewer relapses when studied up to 48 weeks.[15] Rituximab has also been looked at in patients with primary progressive multiple sclerosis in the OLYMPUS trial, in which 439 patients were randomized to receive placebo or rituximab every 24 weeks for a total of 96 weeks. There were no significant differences between rituximab and placebo in terms of time to confirmed disease progression, although in a subgroup analysis, there was a significant difference in a subset of patients who were younger and had an inflammatory component to their disease process.[16] Ocrelizumab, a humanized MCA against CD20 is being studied in MS in phase III trials.

Early studies on natalizumab had shown positive results, which led to two phase III multicenter randomized control studies.

Neuromyelitis optica

Neuromyelitis optica (Devic's disease) is an inflammatory demyelinating disease that attacks the spinal cord and optic nerves. It is associated with more rapid disability than typical multiple sclerosis. A specific antibody against aquaporin-4 channels in the CNS has been found to be highly specific for this disease. There is a prominence of IgG and complement in **neuromyelitis optica (NMO)** lesions, suggesting B cell involvement in pathophysiology. Rituximab has therefore been considered a treatment option. One open label study of eight patients with worsening NMO treated with rituximab showed that six of the eight patients remained attack free during an average time period of 12 months, and the EDSS score improved from a pretreatment score of 7.5 to a score of 5.5 at follow-up.[17] Another retrospective analysis looked at 25 patients, 23 of whom had previously relapsed on other therapies, found that median annualized post-treatment relapse rate went from 1.7 to zero at 19 month follow-up, and median EDSS scores decreased from seven to five after treatment.[18]

Peripheral Neuropathies

Rituximab has also been tried in a number of peripheral neuropathies. In **multifocal motor neuropathy (MMN)**, a rare, symmetric, demyelinating, purely motor neuropathy, approximately 30-50% of patients have been found to have anti-GM1 antibodies in serum, suggesting a role for humoral immunity. IVIG is first line therapy; however some patients have a decreased efficacy over time and therefore require very frequent infusions. Rituximab has been looked at in small case reports in this group of patients, with conflicting results. One case report showed yearly rituximab resulted in reduction of IVIG dosage from every seven days to every 12 days over a five year period,[19] but another showed that in two patients with MMN, one had a decrease in total IVIG dosage while the other required an increase, and there was no significant change in any of the secondary clinical endpoints including strength or sensory improvement, or change in rankin disability scores.[20] In this same study, one patient with sensory ataxic neuropathy related to Sjogren's syndrome was also treated with rituximab and showed a 63% reduction in IVIG dose at one year. Two patients with chronic inflammatory demyelinating polyneuropathy showed no reduction in dose of IVIG needed to maintain remission, however in other case reports its use has appeared more encouraging. [20,21] **Anti-myelin associated glycoprotein (anti-MAG)** neuropathy, a chronic sensorimotor demyelinating polyneuropathy unresponsive to conventional treatments including steroids, plasma exchange, or IVIG is another entity in which rituximab has been tried. A double-blind placebo controlled trial randomizing 13 anti-MAG patients to rituximab, and 13 to placebo, showed that four of 13 patients treated with rituximab showed improvement in leg disability scores whereas zero of 13 placebo patients showed improvement. In addition, there was a significant reduction in time to ten-meter walk in the rituximab group.[22]

Myasthenia Gravis

Myasthenia Gravis, an autoimmune disorder affecting neuromuscular junction transmission is associated with antibodies to nicotinic **acetylcholine receptor (AchR)** in about 80% of cases,

and to **muscle-specific receptor tyrosine kinase** (**MuSK**) in about 10% of cases. In patients difficult to control by conventional therapy rituximab has been tried and described in case reports. One such study looked at three AchR antibody patients and three MuSK antibody patients and showed clinical improvement as well as a significant difference in antibody titers.[23] A controlled trial has yet to be performed, but a further open label pilot study looking at rituximab in refractory myasthenia gravis is currently underway.

Inflammatory Myopathies

The inflammatory myopathies, dermatomyositis, polymyositis, and inclusion body myositis, are also felt to have an association with autoantibodies. First-line treatment is immunosuppressive therapies, beginning with corticosteroids, with up to 70% of patients having an incomplete response. Further treatment with mycophenolate mofetil, methotrexate, cyclosporine and IVIG produces a variable response. This has led to attempts to find further treatment options. Rituximab has been looked at in small open label studies. One such study involved six patients with dermatomyositis and showed clinical improvement in muscle strength, rash, alopecia, and forced vital capacity measurements, correlating with time of B cell depletion by rituximab.[24] Similar results have been found in small open-label clinical trials involving polymyositis.[21] A phase-II, placebo controlled trial looking at rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis is currently underway. Inclusion body myositis remains the most difficult of the inflammatory myopathies to treat. Again, small pilot studies have looked at various monoclonal antibodies as potential therapeutic options. One study of 13 patients with inclusion body myositis treated with alemtuzumab for four days showed a mean decline in total strength over a 12-month period after treatment of 14.9%. In the first six months after treatment, the decline was only 1.9%, corresponding to a 13% differential gain, with four patients showing mean strength gain of 10% when using **Quantitative Muscle Testing** (**QMT**) testing, a measure of strength in kilograms to measure maximum voluntary isometric muscle contractions. In addition, when using the MRC scale, a validated ten-point scale to record strength, after six months of treatment there was a reversal of disease decline, with an average strength gain of 11.4%. On patient self report, five of the 11 patients noticed an improvement in their daily activities.[25] An active ongoing study is underway looking at etanercept, which blocks TNF-alpha, in a double-blind, randomized, placebo-controlled trial to evaluate whether it can delay disease progression.

Conclusion

The potential role of MCA in the treatment of neurological disorders with an inflammatory autoimmune component is become increasingly apparent. Natalizumab is currently the only MCA approved for the treatment of RRMS, but several others are in late stage trials. While the efficacy of monoclonal antibodies in the treatment of RRMS seems to be better than the standard disease modifying agents (Interferons and Glatiramer Acetete), there is a significant concern regarding long term side effects. Ongoing and future trials will further clarify the role of MCA in the treatment of MS and other neurological disorders.

References

1. Goodin DS, Cohen BA, O'Connor P, Kappos L, Stevens JC. Assessment: The use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment subcommittee of the American Academy of Neurology. *Neurology.* 2008;71:766-773.
2. Novak J, Lovett-Racke A, Racke M. Monoclonal antibody therapies and Neurologic Disorders. *Archives of Neurology*. 2008;65(9):1162-1165.
3. Linker R, Kieseier B. Innovative monoclonal antibody therapies in multiple sclerosis. *Therapeutic Advances in Neurological Disorders*. 2008;1(1):33-42.
4. Cree B. Emerging Monoclonal Antibody Therapies for Multiple Sclerosis. *The Neurologist.* 2006;12:171-178.
5. Helliwell C, Coles A. Monoclonal antibodies in multiple sclerosis treatment: current and future steps. *Therapeutic Advances in Neurological Disorders*. 2009;2(4):195-203.
6. Polman C, O'Connor P, Havrdova E, Hutchinson M, Kappos L, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Eng J Med*. 2006;354(9):899-910.
7. Rudick R, Stuart W, Calabresi P, Confavreux C, Galetta S, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Eng J Med*. 2006;354(9):911-923.
8. Coles A, Cox A, Le Page E, Jones J, Trip S, et al. The window of therapeutic opportunity in multiple sclerosis:Evidence from monoclonal antibody therapy. *J Neuro*. 2006;253:98-108.
9. Coles A, Alastair D, Compston S, Selmaj K, Lake S, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Eng J Med*. 2008;359(17):1786-1801.
10. www.clinicaltrials.gov
11. Rose J, Watt H, White A, Carlson N. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neuro*. 2004;56:864-867.
12. Rose J, Burns J, Bjorklund J, Klein J, Watt H, et al. Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. *Neurology*. 2007;69:785-790.
13. Wynn D, Kaufman M, Montalban X, Vollmer T, Simon J, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. *The Lancet Neuurology.* 2010;9(4):381-390.
14. Segal B, Constantinescu C, Raychaudhuri A, Kim L, Fidelus-Gort R, et al. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *The Lancet Neurology.* 2008;7(9):796-804.
15. Hauser S, Waubant E, Arnold D, Vollmer T, Antel J, et al. B cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Eng J Med.* 2008;358(7):676-688.
16. O'Connor H, Freedman M, Calabresi P, Antel J, Simon J, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neuro*. 2009;66(4):460-471.
17. Cree B, Lamb S, Morgan K, Chen A, Waubant E, et al. An open label study on the effects of rituximab in neuromyelitis optica. *Neurology.* 2005;64:1270-1272
18. Jacob A, Weinshenker B, Violich I, McLinskey N, Krupp L, et al. Treatment of neuromyelitis optica with rituximab. *Arch Neuro*. 2008;65(11):1443-1448.
19. Ruegg S, Fuhr P, Steck A. Rituximab stabilizes multifocal motor neuropathy increasingly less responsive to IVIg. *Neurology.* 2004;63:2178-2179
20. Gorson, Natarajan N, Ropper A, Weinstein R. Rituximab treatment in patients with IVIg-dependent immune polyneuropathy: A prospective pilot trial. *Muscle and Nerve* 2007;35:66-69.
21. Kosmidis M, Dalakas M. Practical considerations on the use of rituximab in autoimmune neurological disorders. *Therap Adv Neuro*. 2010;3(2):93-105.
22. Dalakas M, Rakocevic G, Salajegheh M, Dambrosia J, Hahn A, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neuro*. 2009;65(3):286-293.

23. Illa I, Diaz-Manera J, Rojas-Garcia R, Pradas J, Rey A, et al. Sustained response to rituximab in anti-AchR and anti-MuSKpositive myasthenia gravis patients. *J Neuroimmun.* 2008;201-202-:90-94.
24. Levine T. Rituximab in the treatment of dermatomyositis. *Arthritis and Rheumatism.* 2005;52(2):601-607.
25. Dalakas M, Rakocevic G, Schmidt J, Salajegheh M, McElroy B, et al. Effect of alemtuzamab (CAMPATH-1H) in patients with inclusion-body myositis. *Brain*. 2009;132(6):1536-1544.

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Valerie Gendron, MD, is a resident in Neurology at Rhode Island Hospital.

Syed Rizvi, MD, is an Associate Professor of Neurology and Director of the Rhode Island Hospital Multiple Sclerosis Center.

Correspondence

Valerie Gendron, MD
e-mail: vgendron@lifespan.org

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Monoclonal Antibody Use in Inflammatory Bowel Disease

Christopher E. Hayes, MD, and Carolina S. Cerezo, MD

Crohn's disease (CD), ulcerative colitis (**UC**) and **indeterminate colitis** (**IC**) are chronic inflammatory bowel conditions usually collectively referred to as **inflammatory bowel disease** (**IBD**). They appear to be the result of the interaction of genetics, the environment and microbiome of the gastrointestinal tract. The common pathway to intestinal inflammation seems to be immune dysfunction due to lack of balance between pro-inflammatory and anti-inflammatory cytokines.[1]

Tumor necrosis factor alpha (**TNF-α**) has been identified as a key cytokine in the inflammatory cascade of IBD. TNF-α activates and sustains the inflammatory response and is responsible for activating other pro-inflammatory cytokine genes. It also promotes penetration of macrophages, lymphocytes, and neutrophils into inflamed tissues by stimulating the production of cell adhesion molecules by endothelial cells.[1]

Therapeutic targets have focused on immunologic mechanisms that trigger inflammation in IBD. The use of corticosteroids, antibiotics, and anti-inflammatory agents such as **5-aminosalicylates** (**5-ASA**), has improved the management of IBD patients. However, many patients become steroid dependent or resistant and refractory to other agents.

Infliximab

The treatment of moderate-severe CD was revolutionized by the advent of **monoclonal antibodies** (**MAB**) to key cytokines like TNFα. Infliximab (IFX) is a chimeric human/murine monoclonal IgG antibody, which binds TNF-α with high affinity and leads to loss of biological activity. The drug is delivered at initial doses of 5mg/kg in a two-hour intravenous infusion. Induction of remission is attempted with infusions at weeks zero, two, and six, with maintenance therapy doses every eight weeks thereafter if remission is achieved.[2] There is no evidence for further IFX therapy if remission has not been achieved after the three induction doses, known as primary non-response. There is evidence that other monoclonal antibody agents are effective for patients who do not respond to IFX.[3]

Infliximab first showed promise for induction of remission in IBD in the late 1990s. One of the early landmark studies by Targan, et al demonstrated the effectiveness of a single infliximab infusion on clinical status in CD patients with moderate-severe disease who had failed steroid and 5-aminosalicylate therapy[4]. At four weeks post-infusion, 81% achieved clinical response and 33% achieved clinical remission. No difference was identified between groups receiving 5mg/kg and those receiving higher doses. This study and others led to FDA approval of IFX for adult CD in 1998. It was used off-label in pediatrics until it was formally approved for pediatric use in 2006. Infliximab was quickly identified as a rescue and then maintenance therapy for moderate-severe CD in pediatric patients with a variety of significant complications: steroid refractory or steroid dependent disease, penetrating disease (fistulas), and growth failure.[5]

Infliximab is currently indicated for use in luminal CD and fistulizing CD that is resistant to conventional therapies. While conventional therapy is not specifically defined by the FDA, it may include 5-ASA, corticosteroids, antibiotics, solitary enteral feeding, or immunomodulation with methotrexate or **6-mercaptopurine/azathioprine** (**6-MP/AZA**). As **immunomodulators** (**IM**) typically achieve maximal efficacy after three months of use, a minimum of three months is considered as a trial of IM therapy. Surgery is an alternative option prior to initiating IFX, especially for localized disease.[6]

The efficacy of infliximab has been demonstrated in multiple trials.. Hanauer, et al showed that every 8 week maintenance therapy was effective in CD in the **ACCENT I trial** (**A Crohn's disease Clinical study Evaluating infliximab in a New long-term Treatment regimen**).[7] At 30 weeks of use, 39% of those who initially responded to IFX were still in remission. The recent, high profile **Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease** (**SONIC**) trial found that use of IFX at 5mg/kg and given at zero, two, six, and every eight weeks thereafter achieved steroid-free remission for 44.4% of patients at 26 weeks compared to 30.6% (p=0.009) of patients taking azathioprine alone.[8] The highest rate of steroid free remission (56.8%) was

Table 1: Indications for monoclonal antibody use in IBD

	*Crohn's Disease	*Ulcerative Colitis
Moderate-severe disease refractory to steroids	YES	YES
Moderate-severe disease dependent on steroids	YES	YES
Primary induction of remission for moderate-severe IBD	†YES	**NO
Maintenance of remission post response to induction therapy	YES	YES
Reduction in # of fistulizing Crohn's disease:	YES	Not applicable
1. draining enterocutaneous rectovaginal fistula		
2. maintaining fistula closure		

* adult and pediatric patients ** used as a "rescue" agent
† first line agent for penetrating or fistulizing Crohn's disease

Table 2. Side effects associated with monoclonal antibody: anti-TNF therapy

Side effects	Frequency#	Rate per 10,000
Infusion reaction : ie. Fever, rash, anaphylaxis	6.1%*	
Non-Hogkins Lymphoma***	Unknown	
SEER all ages		1.9
IM alone		3.6
Anti-TNF vs SEER		6.3
Anti-TNF vs IM alone		6.3
Death from lymphoma	0.067% (7/10,000)**	
Stop treatment due to adverse event	9.6% (1/10)**	
Death from sepsis	0.4% (4/1,000)**	
Tuberculosis[27]	0.05% (5/10,000)**	

***Siegel CA et al Clin Gastroenterol Hepatol2009
** Siegel CA. Practical Gastroenterology, 2007
* Hoentjen F. World Journal of Gastroenterology, 2009

Frequency of event from systematic analysis (annual)[26]
SEER, Surveillance Epidemiology and End Results Registry
Anti-TNF, anti-Tumor Necrosis Factor
IM, immunomodulators

achieved at 26 weeks with combination therapy of IFX and azathioprine.

An initial debate as to whether IFX should be used for induction of remission only and periodic use thereafter or for maintenance therapy as well has been resolved in favor of long-term use for maintenance of remission.[7] Recent findings from the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry showed that by years 1 through 3 of treatment with IFX, less than 10% of registry patients on maintenance therapy were receiving steroids.[9] In fact, over years one, two, and three after induction with IFX, 26%, 44%, and 33%, respectively, had clinically inactive disease. The available evidence is strong that IFX is efficacious at inducing remission in CD and durable in maintaining remission.

The treatment of fistulizing Crohn's Disease has been a particular concern of gastroenterologists, given the significant morbidity associated with perirectal and intra-abdominal fistulas as well as abscess formation. Present, et al showed that infliximab yielded closure of 50% or more of draining enterocutaneous fistulas in 68% of study patients.[10] The study also showed closure of all fistulas in 55% of study patients. Another pivotal study was **ACCENT II** (**A Crohn's disease Clinical study Evaluating infliximab in a New long-term Treatment regimen in patients with fistulizing Crohn's disease**), where Lichtenstein, et al showed IFX maintenance use for fistulizing CD resulted in significantly fewer hospitalizations and surgeries.[11] The use of **thiopurines** (**6-MP/AZA**) for fistulas typically yield more modest benefit and IFX is now considered preferable for fistulizing CD.

Nearly 80% of patients with Crohn's Disease ultimately require surgical bowel resection.[12] While resections effectively palliate recalcitrant inflammation, reoperation rates for recurrent disease are significant: 10-35% at five years, 20-45% at ten years, and 45-50% at 20 years. A recent meta-analysis of clinical trials reporting on surgical outcomes from CD found a strong association between endoscopic findings of inflammation at 6 months after surgery and the clinical recurrence rate at one year after surgery.[13] Available evidence is strong that IFX is efficacious for prevention of recurrence after surgery for CD. By controlling early recurrence of inflammation, IFX use after surgical resection may alter the natural history of the progression of CD and lower reoperation rates.

Growth failure is a common feature of uncontrolled IBD in children, and resumed growth trajectory indicates good disease control. Walters, et al showed improved linear growth on IFX in a subset of chronically active CD who had growth failure despite steroid and IM use.[14]

While infliximab has been in use for moderate-severe Crohn's Disease since the late 1990s, strong evidence for use in ulcerative colitis has been more recent. The **Active Ulcerative Colitis Trials 1 and 2** (**ACT 1 and ACT 2**) were randomized, double blind, placebo-controlled trials that studied the efficacy of IFX for induction and maintenance therapy for adults with UC.[15] At eight weeks, 69% had a clinical response as compared with 37% who had received placebo. At week 54, 45% of patients had clinical response as compared with 20% who had received placebo. These important studies established IFX as efficacious for moderate-severe UC and, as in use with CD, 5mg/kg dosing was equally efficacious as higher dosing.

Given the establishment of infliximab as a powerful therapy for moderate-severe, complicated CD and UC, its proper place in the hierarchy of medical therapies for Inflammatory Bowel Disease has been a matter of debate among gastroenterologists. The more conservative approach has been so-called "step-up" therapy, in which traditional therapies are exhausted first before moving on to IFX. Initially, patients were managed nearly uniformly with 5-ASA compounds for maintenance and steroids for episodic flare-ups. If this proved unsuccessful, the addition of an immunomodulator (IM) such as 6-MP/AZA or methotrexate was then attempted first before contemplating the use of IFX.[6]

Patients with refractory disease typically started infliximab for induction and maintenance therapy while on an IM and continued use of both medications as combination therapy. One of the benefits of combination therapy was the prevention of antibody formation against IFX, which leads to drug reactions and loss of response.[16] A recent trial comparing combination therapy with either IFX or an IM alone showed that combination therapy yields superior clinical outcomes.[8]

Given the evidence that infliximab and other monoclonal antibody medications are superior to more traditional IBD therapies, is generally well-tolerated, and may reduce a patient's need for surgery, there is current movement in the field of

Table 3. Monoclonal Antibody Agents Used for Inflammatory Bowel Disease

Agent	Mechanism of Action	Indication
Infliximab	Binds/inactivates TNFα, blocks inflammatory cascade	Moderate-severe IBD, refractory to conventional therapy
Adalimumab	Binds/inactivates TNFα, blocks inflammatory cascade	Moderate-severe IBD, refractory to conventional therapy; failure of infliximab therapy
Certolizumab	Binds/inactivates TNFα, blocks inflammatory cascade	Moderate-severe IBD, refractory to conventional therapy; failure of infliximab therapy
Natalizumab	Binds/inactivates integrin molecules → prevents migration of inflammatory cells to tissue	Moderate-severe IBD, refractory to conventional therapy; failure of infliximab therapy

gastroenterology toward so-called "top-down" therapy. In other words, IFX and other monoclonal antibody agents would be utilized early in the disease course for moderate-severe disease.[17]

This approach is controversial largely due to our short experience with using IFX and other monoclonal antibody agents and the known serious side effects identified thus far. There is a black box warning on IFX for reactivation of tuberculosis, and this is regularly screened for prior to and throughout a patient's course on IFX or other monoclonal antibody agents. There is a risk of infusion reactions of 6.1%.[18] As anaphylaxis is a possibility, infusion of IFX is carefully monitored in the clinical setting. More common infusion reactions are fever, rash, dizziness, hypertension, myalgias or arthralgias. The overall risk of infection is between 0.3% – 0.9%, the majority of which were pneumonias but sepsis, cellulitis and viral infections have also been noted. The risk of developing a serious infection while on IFX is 4.4 times that of a person not on immune suppression, and increases to 14.5 the risk when on a concomitant immune suppressive drug such as steroids or IM.[18] Significantly, the risk of death from sepsis is 4/1,000 patient years (0.4%).[19]

The risk that gives most patients and provider pause is the risk of lymphoma. In a meta-analysis of 8905 patients representing 20,602 patient years, Siegel and colleagues reported that the risk of non-Hodgkin lymphoma with use of IM alone is 3.6/10,000 versus 6.3/10,000 with IFX use (Table 2).[19] With IFX use, the risk of dying from a lymphoma is seven per 10,000 IFX treated patient (0.067%).[20] These lymphomas are usually responsive to treatment. Out of the over one million patients treated with monoclonal antibody agents worldwide, 27 cases of the uniformly fatal **Hepato-Splenic T-cell Lymphoma** (**HSTL**) have been reported. In the 25 cases where data on 6-MP/AZA use was available, all 25 patients had exposure to these medications. These patients were not necessarily taking the two agents concomitantly.[21] It is not known whether the risk for this exceedingly rare lymphoma lies in monoclonal antibody use, 6-MP/AZA use, or the combination. While the overall risk of these serious complications is small compared to known complications in IBD patients sick enough to warrant IFX use, the risk is significant enough to alter patients' acceptance of the drug and in some cases alter physician prescribing patterns.

Other MAB used in the treatment of IBD

Other monoclonal antibody agents currently approved for use in IBD are adalimumab, certolizumab, and natalizumab. Adalimumab is a fully humanized monoclonal antibody to TNFα, and is given subcutaneously on a biweekly basis. Certolizumab is a humanized antibody fragment to TNFα. Natalizumab is a monoclonal antibody against integrin molecules, which are involved in attracting inflammatory cells to tissues. None of these have been shown to be more effective than infliximab at this time, and are usually used either after a patient has lost response to infliximab or if the medicine is not tolerated.

Adalimumab has been shown to be effective for induction and maintenance of remission in CD. In the **CLASSIC I trial (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease)**, rates of remission at four weeks of use were as high as 36% utilizing dosing at zero and two weeks of 160mg and 80mg, respectively.[22] The CLASSIC II trial further showed that adalimumab is effective for maintenance of remission. 55 patients who had achieved remission by week four of adalimumab use were enrolled and randomized to receive either adalimumab every week, every other week, or placebo. The rates of remission at week 56 of the trial were 83%, 79%, and 44%, respectively.[23] The CHARM trial (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance) also showed promising evidence for adalimumab maintenance therapy for moderate-severe CD. Those who initially responded to the medicine showed continued remission at week 56 of about 40%, three times the rate of those in the placebo group.[24]

There is evidence that adalimumab can be used effectively despite loss of response to IFX therapy. In the **RESEAT study (Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy)** in pediatric patients, of whom 95% had previously lost response to IFX therapy, clinical response by physician global assessment at three, six, and 12 months of use was 65%, 71%, and 70%, respectively. Steroid-free remission was achieved at three, six, and 12 months by 22%, 33%, and 42% of patients, respectively.[25]

Conclusion

Monoclonal antibody therapies that target mediators of inflammation have shown remarkable efficacy in inducing and maintaining remission in moderate-severe IBD. They show the promise not only of clinical wellness, but also of the potential to change the natural history of IBD by postponing the need for surgery. While the preponderance of evidence to date is with the use of infliximab, further study of the

proper use of other monoclonal antibody therapies could provide for better therapeutic options and health outcomes for those with moderate-severe IBD.

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References

1. Owczarek D, Cibor D, Szczepanek M, Mach T. Biological therapy of inflammatory bowel disease. *Polskie Archiwum Medycyny Wewnetrznej*. 2009;119(1-2).
2. Physician's Desk Reference. *59th ed*. Montvale, NJ*: Medical Economics*. 2005.
3. Sandborn WJ, Rutgeerts P, Enns R, Pollack PF, *et al.* Adalimumab induction therapy for Crohn's disease previously treated with infliximab: a randomized trial. *Ann Intern Med*. 2007;146:829–38.
4. Targan SR, Hanauer SB, van Deventer SJH, Rutgeerts PJ, et al. A Short-Term Study of Chimeric Monoclonal Antibody cA2 to Tumor Necrosis Factor ∝ for Crohn's Disease. *N Eng J Med*. 1997;337 (15):1029–35.
5. Vasiliauskas EA, Thomas DW, Schaffer S, Targan SR, et al. Collaborative Experience of Open-Label Infliximab in Refractory Pediatric Crohn's Disease. *Journal of Pediatric Gastroenterology & Nutrition*. 1999;29(4):525.
6. St. Charles M, Weiss Smith SR, Beardsley R, Cross RK, et al. Gastroenterologists' Prescribing of Infliximab for Crohn's Disease: A National Study. *Inflammatory Bowel Disease*. 2009;15(10):1467–75.
7. Hanauer SB, Feagan BG, Lichtenstein GR, Rutgeerts P, and the ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet*. 2002;359(9317):1541–9.
8. Colombel JF, Sandborn WJ, Reinisch W, Rutgeerts P, et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *N Eng J Med*. 2010;362(15):1383–95.
9. Hyams JS, Leher T, Griffiths A, Markowitz J and the Pediatric Inflammatory Bowel Disease Collaborative Research Group. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflammatory Bowel Disease*. 2009;15(6):816–22.
10. Present DH, Rutgeerts P, Targan S, van Deventer SJH, et al. Infliximab for the Treatment of Fistulas in Patients with Crohn's Disease. *N Eng J Med*. 1999;340: 1398–1405.
11. Lichtenstein GR, Yan S, Bala M, Blank M, and Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedure in fistulizing Crohn's disease. *Gastroenterology*. 2005;128(4):862–9.
12. Yamamoto T. Factors affecting recurrence after surgery for Crohn's disease. *World Journal of Gastroenterology*. 2005;11(26):3971–9.
13. Yamamoto T. Prevention of recurrence after surgery for Crohn's disease: Efficacy of infliximab. *World Journal of Gastroenterology*. 2010;16(43): 5405–10.
14. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. *Inflammatory Bowel Disease*. 2007; 13(4): 424–30.
15. Rutgeerts P, Sandborn WJ, Feagan BG, Colombel JF, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. *N Eng J Med*. 2005;353(23):2462–76.
16. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Eng J Med*. 2003;348(7):601–8.
17. Velayos FS, Sandborn WJ. Positioning biologic therapy for Crohn's disease and ulcerative colitis. *Current Gastroenterology Reports*. 2007;9(6): 521–7.
18. Hoentjen F, Bodegraven AV. Safety of anti-tumor necrosis factor therapy in inflammatory bowel disease. *World Journal of Gastroenterology*. 2009;15(17):2067–73.
19. Siegel CA, et al. *Clin Gastroenterol Hepatol.* 2009;7:874–81
20. Siegel CA. Guide to Discussing the Risk of Immunomodulator and Anti-TNF Therapy with Inflammatory Bowel Disease Patients. *Practical Gastroenterology*. 2007;XXXI (11):14–24.
21. Janssen Biotech, Inc. Medical Information Services, Inquiry #1-1313975908, Data on File, October 25, 2011.
22. Hanauer SB, Sandborn WJ, Rutgeerts P, Pollack P, et al. Human Anti-Tumor Necrosis Factor Monoclonal Antibody (Adalimumab) in Crohn's Disease: the CLASSIC-I Trial. *Gastroenterology*. 2006;130:323–33.
23. Sandborn WJ, Hanauer SB, Rutgeerts P, Pollack PF, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007;56:1232–9.
24. Colombel JF, Sandborn WJ, Rutgeerts P, Pollack PF, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52–65.
25. Rosh JR, Lerer T, Markowitz J, Hyams JS, et al. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in Pediatric Crohn's Disease. *Gastroenterology*. 2009;104:3042–9.
26. Siegel CA, Hur C, Korzenik JR, et al. Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol.* 2006:4(8):1017–24.
27. Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum*. 2004;50(2):372–9.

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Christopher E. Hayes, MD, is a senior fellow in Pediatric Gastroenterology, Nutrition and Liver Diseases at Hasbro Children's Hospital.

Carolina S. Cerezo, MD, FAAP, is an Assistant Professor of Pediatrics (Clinical) at the Warren Alpert Medical School of Brown University and a full-time pediatric gastroenterologist at Hasbro Children's Hospital.

Correspondence

Carolina S. Cerezo, MD, FAAP
Division of Pediatric Gastroenterology, Nutrition and Liver Diseases
Hasbro Children's Hospital
593 Eddy Street, MPH 131
Providence, RI 02903
e-mail: Carolina_Cerezo@brown.edu

Preventable Death: Accidental Drug Overdose in Rhode Island

Traci C. Green, MSc, PhD, and Edward F. Donnelly, RN, MPH

Rhode Island is in the midst of a drug poisoning epidemic. Since 2005, the number of drug poisoning deaths has exceeded the number of motor vehicle accidents, falls, firearms, and fire death among adults <85 years of age.[1] However, Rhode Island is not alone: 20 states now report similar statistics where drug poisonings dominate adult injury deaths.[1] National survey data find that Rhode Island has the nation's highest rate of past month illicit drug use [2], and nonmedical use of prescription pain pills ranks 3rd in the country, behind Oklahoma and Oregon.[3]

The mechanism of death from overdose is respiratory depression, which deprives the victim's brain of oxygen, causing death over a period of one to three hours.[4] Proximal causal mechanisms and risk factors for accidental overdose include: (a) change in tolerance (i.e. due to voluntary or forced abstinence such as hospitalization, imprisonment, detoxification, self-imposed abstinence); (b) mixing opioids with other substances, especially central nervous system depressants like alcohol or benzodiazepines which worsen respiratory depression; (c) presence of illness, especially diseases that may affect drug metabolism such as hepatitis C or HIV, and breathing conditions like pneumonia or sleep apnea; and (d) using opioids alone, in the absence of others who may recognize a victim's symptoms and act to intervene.

Like all injuries, the majority of drug poisoning deaths are preventable. This surveillance brief provides an overview of state-level statistics describing the extent and nature of the drug poisoning epidemic in Rhode Island and will conclude with a summary of the local prevention initiatives being undertaken or considered.

Methods

This report draws from data collected from 2005 to 2009 by the **Rhode Island Department of Health** (**HEALTH**) in its annual census of **emergency department** (**ED**) visits and hospitalizations, as well as from the **Drug Abuse Warning Network** (**DAWN**) medical examiner report, in which Rhode Island participated for the year 2008.[5] Unintentional poisonings—or overdoses—were identified using the following ICD-9 CM Codes: 960-979 and E Codes: E860-E869, E980. We employ a surveillance-oriented definition of drug overdose, which includes events of unintentional and undetermined intent. Here we report, but do not focus on, intentional poisoning events—or suicides by poisonings—as their etiology is both well described in the literature (c.f.,[6]) and markedly different from poisonings that are accidental in manner. Summary data are reported (count, proportion) for all poisonings. Demographics of the injury victims (age, sex, and race/ethnicity) are reported for unintentional/undetermined poisoning ED visits and hospitalizations.

Results

From 2005 to 2009, there were 19,733 ED visits for drug poisonings. Of these 10,404 (52.7%) were unintentional intent, another 2,047 (10.4%) were undetermined intents, and the remainder were determined to be either self-inflicted (i.e., intentional 36.6%, n=7,216) or due to assault or legal intervention (less than 1%, n=65).

The number and proportion of poison visits of unintentional/undetermined intents remained constant over the 2005-2009 time period (Figure 1). With unintentional visits hovering

Table 1: Unintentional and undetermined poisoning emergency department visits and hospitalization discharges, 2005-2009, Rhode Island

		Emergency Department Visits		Hospitalization Discharges	
		#	%	#	%
RACE	White	9735	78.2	2109	83.1
	Black	944	7.6	169	6.7
	American Indian*	21	0.2	3	0.1
	Asian	119	1.0	20	0.8
	Hispanic	1192	9.6	162	6.4
	Other	153	1.2	31	1.2
	Unknown	280	2.3	44	1.7
TOTAL		12444	100.0	2538	100.0
SEX	Male	6335	50.9	1322	52.1
	Female	6111	49.1	1216	47.9
TOTAL		12446	1.0	2538	1.0
AGE GROUP	<15	2742	22.0	194	7.6
	15-24	1999	16.1	285	11.2
	25-34	1718	13.8	259	10.2
	35-44	1891	15.2	410	16.2
	45-54	1849	14.9	523	20.6
	55-64	1026	8.2	325	12.8
	65+	1221	9.8	542	21.4
TOTAL		12446	100	2538	100

*No data available for American Indian undetermined discharges.
Note, denominators may represent multiple visits by the same individual. Total counts may differ slightly based on availability of demographic data.

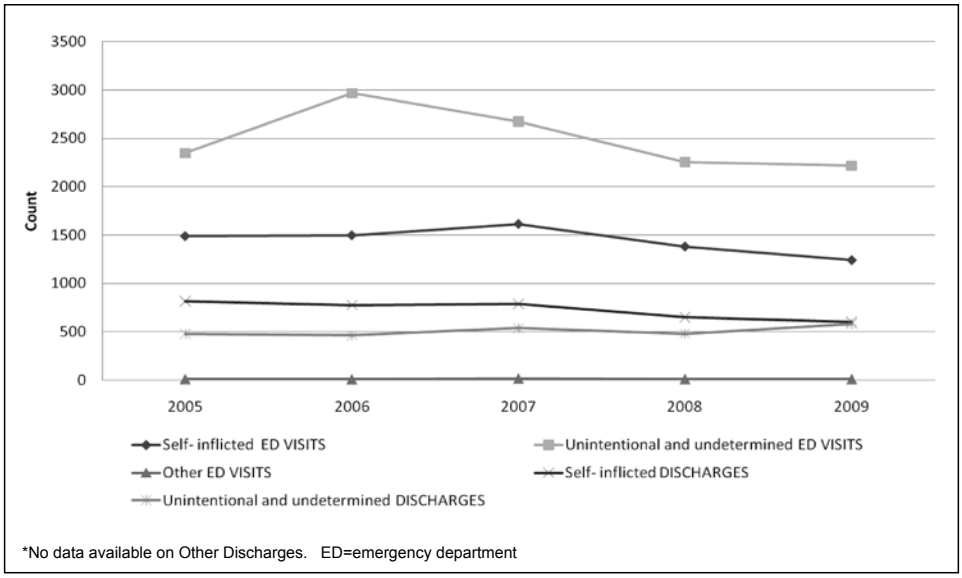

Figure 1. ED Visits and Hospital Discharges by Intent of Admission by Year, Rhode Island, 2005–2009.*

around 2,000 per year and undetermined around 375 per year, together ED visits for accidental overdose comprise approximately 63% of all ED visits for poisonings. In contrast, during this same time period, hospitalizations for poisonings were more frequently for self-inflicted poisonings (58.8%, n=3,629) than for unintentional/undetermined poisonings (41%, n=2,538).

There were 193 drug-related deaths in Rhode Island in 2008; the vast majority of which were accidental overdoses. Accidental overdoses tended to involve opioids such as prescription opioid analgesics or heroin. For the year 2008, the ratio of ED accidental poisoning visits to fatal overdoses was 12:1. This ratio stands in sharp contrast to ED visits and deaths for intentional poisoning injuries. The ratio of intentional poisoning ED visits to deaths was 41:1. The very high proportion of deaths resulting from accidental poisoning-when compared to self-inflicted poisoning injuries-reflects the extreme lethality of overdose. In 2008, there were nearly twice as many accidental overdose events admitted to the ED (n=2251) than intentional poisoning events admitted to the ED (n=1380) but there were more than five times the number of deaths due to accidental overdose than due to intentional poisoning (193 vs. 34).

Table 1 presents the demographics of victims admitted to the ED or hospitalized for accidental overdose. The predominant demographic of the accidental overdose victim presenting to the ED is that of a White male or female. Similar proportions of men and women appear to present to the ED for care for accidental overdose events and Whites represent more than three-quarters of unintentional poison visits. A notable minority of victims are Hispanic (9.6%) or Black (7.6%). Hospitalizations for accidental overdose events reflect largely comparable demographic patterns. Age distinguishes nonfatal from fatal overdose victims. Thirty-eight percent (38%) of ED visits for accidental overdose events are among those under age 25; another 43.4% are age 25-54, with the remaining 18% aged 55 or older. In contrast, decedents of accidental overdose are predominantly aged 35-54.[5] The difference in age may reflect lack of comorbidities, less severe addiction, a more social orientation of drug use, or some other explanation differentiating younger from older users.

Discussion

State-level data indicate consistently high counts of ED visits and hospitalizations due to accidental overdose. Demographically, these poor health outcomes afflict adults at the prime of their life, causing premature death.

Injury epidemiology has expanded public health science by conceptualizing injuries as preventable and controllable. Over the past 50 years, concerted efforts by industry, government, citizens action groups, and individuals have made driving a car a much safer, more common, and more enjoyable experience. Today, the reduction of motor vehicle accident fatalities is regarded as one of the great 20th Century public health accomplishments. Currently we are at a similar crossroads of epidemic overdose deaths, with a complicated and complex set of factors and competing health interests.

In Rhode Island, recent efforts may provide some promise in changing the course of this epidemic. Because national and local statistics indicate that opioid analgesics are driving the increase in overdose deaths, many approaches focus on safer prescribing and altering the accessibility of medications. HEALTH maintains a **prescription monitoring program** (**PMP**) containing information on patients prescribed controlled substances such as opioid analgesics. Data are accessible to registered health professionals and law enforcement only. Health professionals may also use the report as an opportunity to discuss with the patient how to reduce the risk of adverse events, such as overdose, and other prevention education such as proper medication storage and disposal. By early 2012, the PMP will offer real-time electronic access. HEALTH is also considering requiring two hours of continuing medical education for controlled substance license holders. In the community, the Miriam Hospital's **PONI** (**Preventing Overdose and Naloxone Intervention**) program provides training in overdose recognition and naloxone (Narcan), the standard antidote for reversing opioid overdoses, to

Table 2: PONI overdose prevention and response training components

Training Component
Identification of an opioid overdose
Checking for response and breathing
Calling 911 with the report that the victim is not breathing
Conducting rescue breathing
Administering naloxone (Narcan) and monitoring victim's response

people who may experience or witness an overdose.[7] PONI curriculum components are given in Table 2. Over 150 people in the community and, due to their extreme fatal overdose risk,[8] over 1,500 prisoners, have been trained through PONI. The statistics presented in this surveillance report suggest that health-care institutions may also be important targets for expanding prevention interventions. Finally, two current research studies involve overdose prevention. In a Centers for Disease Control and Prevention-funded study, Rhode Island Hospital researchers are exploring how PMPs can reduce prescription opioid overdose death. At the Miriam and Rhode Island Hospitals, a National Institute on Drug Abuse-funded study will test the feasibility of providing a prison-specific overdose prevention and response video and prescribed naloxone at release for prisoners.

In conclusion, accidental poisonings exact far-reaching, costly, and lethal consequences in Rhode Island. This epidemic rages unabated, and will continue to grow absent a concerted, comprehensive public health response. Preventive measures are needed and existing, effective interventions need to be scaled-up to better control the outcome of these preventable injuries. A state-wide, multiagency, and multipronged approach is indicated to effectively address Rhode Island's drug poisoning epidemic.

References

1. Centers for Disease Control and Prevention. WISQARS: Leading Causes of Death Reports, 1999-2007. 2007; http://webappa.cdc.gov/sasweb/ncipc/leadcaus10.html. Accessed Sept 11, 2011, 2011.
2. SAMHSA. *State Estimates of Substance Use from the 2007-2008 National Surveys on Drug Use and Health.* Rockville, MD: HHS Publication No. SMA 10-4472;2010.
3. SAMHSA. *State Estimates of Substance Use and Mental Disorders from the 2008-2009 National Surveys on Drug Use and Health.* Rockville, MD: HHS Publication No. (SMA) 11-4641;2011.
4. Sporer KA. Acute heroin overdose. *Ann Intern Med.* Apr 6 1999;130(7):584-90.
5. SAMHSA. *Area Profiles of Drug-Related Mortality, 2008.* Rockville, MD, 2010.
6. NIMH. Suicide in the U.S.: Statistics and Prevention. 2011; http://www.nimh.nih.gov/health/publications/suicide-in-the-us-statistics-and-prevention/index.shtml. Accessed Sept 1, 2011.
7. Yokell M, Green TC, Bowman S, McKenzie M, Rich J. Opioid Overdose Prevention and Naloxone Distribution in Rhode Island. *Medicine Health Rhode Island.* 2011;94(8):240–2.
8. Merrall EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction.* Sep 2010;105(9):1545–54.

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Traci C. Green, MSc, PhD, is Assistant Professor of Medicine and Epidemiology, Brown Medical School, at the Rhode Island Hospital, Division of General Internal Medicine.

Edward F. Donnelly, RN, MPH, is a Senior Public Health Epidemiologist in the Center for Health Data and Analysis at the Rhode Island Department of Health.

Correspondence

Traci Craig Green, MSc, PhD
Rhode Island Hospital
111 Plain St. Building, Rm 111
Providence, RI 02903
phone: (401) 444-3845
fax: (401) 444-5040
e-mail: traci_green@brown.edu

The Warren Alpert Medical School of Brown University
Brown
QUALITY PARTNERS OF RHODE ISLAND
Division of General Internal Medicine Department of Medicine
QUALITY CARE AND PATIENT SAFETY FOR THE PRACTICING PHYSICIAN
Quality Partners of RI
Sarita Warrier, MD, and Brian McGillen, MD, Co-editors

Improving Physician Hand-offs

Sarita Warrier, MD

The Scope of the Problem

In 2003, the **Accreditation Council for Graduate Medical Education (ACGME)** required residency programs to abide by new work hour regulations, limiting physician work hours to 80 per week. In order to accommodate these changes, residency programs had to rethink how they provided 24-hour care to patients. The use of night floats and coverage shifts increased, and in the process, the number of hand-offs (transfer of patient care responsibilities) also increased. With each hand-off, there exists the potential for medical error and a threat to patient safety. Patients are worried: in one study,[1] 28% of patients reported concerns about how often hand-offs of care occurred. In this same study, patients' "worries about fatigue/discontinuity" were significantly associated with trust in and satisfaction with the health care provider. Patient worries are compounded by the fact that physicians have difficulty gauging the effectiveness of their own communication. A study of the sign-out process[2] noted that "the most important piece of information about a patient was not successfully communicated 60% of the time," while in a survey of pediatrics residents,[3] 73% noted uncertainty regarding care plans due to incomplete verbal hand-offs, and only 19% reported that written sign-outs were accurate with respect to patient information and care plans. Due to these concerns, The Joint Commission implemented a **National Patient Safety Goal (NPSG)** in 2006 that encouraged health care organizations to adopt standardized hand-offs. In 2010, this NPSG became a requirement for accreditation. Despite this requirement, hand-offs still remain a source for error and a threat to patient safety, as an estimated 80% of serious medical errors involve miscommunication between caregivers during patient hand-offs.[4]

Potential Solutions

Several themes emerge in the literature about hand-offs. The first, unfortunately, is that better quality studies are needed. A recent review[5] of the literature attempted to identify effective features of handoffs, but was limited by the small number of research studies including measures of effectiveness (only six of the 18 studies reviewed included effectiveness measures). However, the information available suggests some common strategies that may improve hand-off communications: two-way/two-level communication, standardization, and computerization.

One common strategy is that successful hand-offs require two-level, two-way communication. Receiving physicians prefer two levels of information—written and verbal sign-out. While one study[6] reported that residents felt the number of data items in formal, written data summaries may obscure the critical information necessary for actual patient management, and found that the use of data summaries was associated with an increased odds ratio for errors, it was also noted that data summaries improved efficiency. This study also noted that while resident physicians preferred verbal, interactive hand-offs, the number of asynchronous hand-offs (written sign-outs without face-to-face interaction) was increasing. The opportunity for the recipient of sign-out to ask questions and obtain clarifications, particularly regarding "to-do lists" or responses to unexpected events, enhances the hand-off process, and is integral to ensuring a safe transfer of responsibility.

The second common strategy is the standardization of hand-off information. There is a variety of available tools (and mnemonics) to help with this process. The best studied is the **SBAR (Situation-Background-Assessment-Recommendation)** technique,[7] which standardizes critical patient information into an organized summary that is conveyed in the same order, every time. Given its brevity, SBAR is particularly useful for the verbal component of the hand-off—clinical information distilled to key points. The written hand-off component often includes more detailed information, but should be standardized as well. One proposed mnemonic for written hand-off standardization is **ANTICipate (Administrative data-New infomation-Tasks-Illness-Contigency planning)**,[8] which includes only the pertinent information for the safe transfer of patient care. In fact, the creators of this mnemonic specifically note that certain information—initial history and physical exam, completed tasks, discharge summary information—are *not* essential to the sign-out process and need not be included in the written sign-out document. Another studied mnemonic is **SIGNOUT? (Sick or DNR-Identifying data-General hospital course-New events-Overall health-Upcoming possibilities-Tasks to complete-?Questions)**,[9] a brief, structured tool modeled after the SBAR, which may be flexible enough to be used as either a written or verbal hand-off guide. The goal of both of these tools is to convey the critical patient care information necessary for safe, effective hand-offs in an organized and accessible format.

The final common strategy is computerization of hand-off information, which works in three ways. First, the use of templates allows for standardization of the information contained in hand-offs. Standardized fields for input (either resident-supplied or auto-populated information from a connected hospital information system) ensure that key components are always communicated (identifying data, code status, hospital course, etc.). Second, computerization can allow for more accurate, up-to-date information, particularly if the hand-off tool is linked to an electronic medical record. Third, computerization allows for improved efficiency, as saved or auto-populated information reduces the need for resi-

dents to recopy information. A recent study[10] of a computerized rounding and sign-out system showed that the system reduced rounding time and decreased repetitive information-handling tasks by residents without increasing deviations from expected care, resident-reported overnight events, or adverse drug events.

Future Directions

Given the many areas in need of improvement in physician hand-offs, the multitude of potential strategies available, and the ever-changing landscape of medical education, there are several future areas of study for improving safety in hand-offs. The Joint Commission Center for Transforming Healthcare released their strategies for Improving Hand-off Communications in 2010.[4] This package contains targeted solutions for specific causes of ineffective hand-offs, and has shown a 52% reduction in "defective" hand-offs at the project programs that have fully implemented these solutions. This project is currently in the pilot testing phase at other hospital systems.

Another area of future study is physician training in hand-off communications. There has been a lack of formal instruction for medical students and residents in the skill of hand-off communication. In the last few years, some progress has been made in developing curricula and training exercises. One study piloted a simulated hand-off experience for medical students, which was well-received by the students.[11] Another program created a hand-off curriculum for interns which resulted in improved spoken and written sign-out skills.[12] These are just a few areas of active study on the national scene. Locally, Rhode Island Hospital and Hasbro Children's Hospital are in the early phases of a study investigating resident physician sign-out.

A recent commentary[13] suggests that making sign-out part of the official medical record, particularly in systems with electronic health records, would improve patient safety. First, it would help encourage standardization of hand-off information, and allow for more up-to-date clinical information to be universally available to other providers (nurses, respiratory therapists, etc.) caring for the patient. Second, it would encourage electronic health record vendors to create support tools for sign-out, which may enhance clinical decision making, acting as additional protection for the patient. This remains an area of ongoing study.

Physician hand-offs remain an important potential source for medical errors and potential threat to patient safety. Through training of physicians, standardization and computerization of hand-offs, and improvement in communication skills, the physician community can improve patient hand-offs, and create a safer climate for patient care.

References:

1. Fletcher KE, Wiest FC, Halasyamani L, et al. How Do Hospitalized Patients Feel About Resident Work Hours, Fatigue, and Discontinuity of Care? *J Gen Intern Med.* 2007;23(5):623–8.
2. Chang VY, Arora VM, Lev-Ari S, D'Arcy M, Keysar B. Interns Overestimate the Effectiveness of Their Hand-off Communication. *Pediatrics.* 2010;125:491–6.
3. McSweeney ME, Lightdale JR, Vinci RJ, Moses J. Patient Handoffs: Pediatric Resident Experiences and Lessons Learned. *Clinical Pediatrics.* 2011;50(1):57–63.
4. Storyboards for the Hand-off Communications Project. The Joint Commission Center for Transforming Healthcare. Available at http://www.centerfortransforminghealthcare.org/projects/display.aspx?projectid=1. Accessed September 18, 2011.
5. Riesenberg L, Leitzsch J, Massucci JL, et al. Residents' and Attending Physicians' Handoffs: A Systematic Review of the Literature. *Acad Med.* 2009;84:1775–87.
6. Philibert I. Use of strategies from high-reliability organisations to the patient hand-off by resident physicians: practical implications. *Qual Saf Health Care.* 2009;18:261–6.
7. SBAR technique for communication: A Situational Briefing Model. Institute for Healthcare Improvement. Available at http://www.ihi.org/knowledge/Pages/Tools/SBARTechniqueforCommunicationASituationalBriefingModel.aspx. Accessed September 21, 2011.
8. Vidyarthi AR, Arora V, Schnipper JL, Wall SD, Wachter RM. Managing Discontinuity in Academic Medical Centers: Strategies for a Safe and Effective Resident Sign-out. *Journal of Hospital Medicine.* 2006;1:257–66.
9. Horwitz LI, Moin T, Green ML. Development and Implementation of an Oral Sign-out Skills Curriculum. *J Gen Intern Med.* 2007;22(10):1470–4.
10. Van Eaton EG, McDonough K, Lober WB, et al. Safety of Using a Computerized Rounding and Sign-out System to Reduce Resident Duty Hours. *Acad Med.* 2010;85:1189–95.
11. Farnan JM, Paro JAM, Rodriguez RM, et al. Hand-off Education and Evaluation: Piloting the Observed Simulated Hand-off Experience (OSHE). *J Gen Intern Med.* 2009;25(2):129–34.
12. Gakhar B, Spencer AL. Using Direct Observation, Formal Evaluation, and an Interactive Curriculum to Improve the Sign-out Practices of Internal Medicine Interns. *Acad Med.* 2010;85:118–8.
13. Stein DM, Stetson PD. Commentary: Time to Sign Off on Signout. *Acad Med.* 2011;86:804–6.

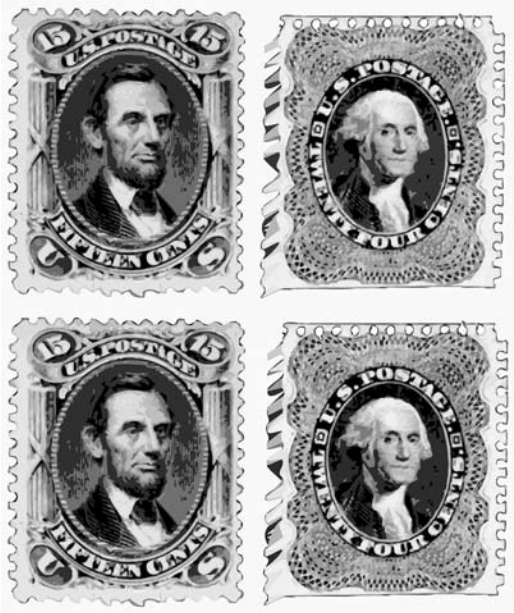
Disclosure of Financial Interests

The author and/or spouse/significant other have no financial interests to disclose.

Sarita Warrier is an Assistant Professor of Medicine (Clinical) at the Alpert Medical School at Brown University, and an attending physician in the Division of General Internal Medicine at Rhode Island Hospital.

Correspondence

Sarita Warrier, MD
Jane Brown Ground 0105
593 Eddy Street
Providence, RI 02903
e-mail: swarrier@lifespan.org



Information for Contributors

Medicine & Health/Rhode Island is peer-reviewed, and listed in the *Index Medicus*. We welcome submissions in the following categories:

Contributions
Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be submitted as separate electronic files (jpeg, tif, or pdf). Each submission should also be accompanied by a short (100-150 words) abstract.

Creative Clinician
Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

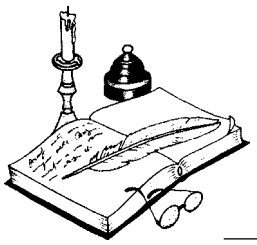
Point of View
Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

Advances in Pharmacology
Authors discuss new treatments. Maximum length: 1200 words.

Advances in Laboratory Medicine
Authors discuss a new laboratory technique. Maximum length: 1200 words.

Images in Medicine
Authors submit an interesting Image, with a 300-400 word explanation.

For the above articles: Please submit an electronic version (Microsoft Word or Text) with the author's name, mailing address, phone, fax, e-mail address, and clinical and/or academic positions to the managing editor, John Teehan, e-mail: jdteehan@rimed.org. For additional information, phone: (631) 903-3389. Faxes may be sent to (401) 826-1926.



Physician's Lexicon

The Pt-vehicles, Ancient and Modern

Long before the American Navy introduced rapidly maneuverable patrol-torpedo vessels (called PT Boats) the ancient Greeks had infiltrated their vocabulary with words beginning with the improbable combination of letters 'P' and 'T'.'

Ptarmic, for example, is an adjective meaning a susceptibility to sneezing. And Ptarmica is the botanical genus for what is colloquially called, sneezewort. (The family of arctic grouse called ptarmigan, however, gets its name from a Gaelic word meaning croaker.)

The Greek prefixes, *pteno-*, *ptero-* and *pterygo-* begin words describing things that are feathered, winged or capable of flight; or, remotely, something that falls from flight. Thus an extinct flying reptile is named pterodactyl, with the *dactyl* root meaning toe or finger (as in dactylogram, an earlier word for fingerprint.) A pteropus is a genus of fruit bats (literally, wing-footed.) And pterygoid is an adjective meaning winglike. And an aircraft called helicopter is one that employs rotating blades to achieve flight (*helico-*, Greek for spiral.)

Ptomaine, nitrogenous substances generated in the process of putrefaction and often poisonous, is a word coined by the Italian chemist Francesco Selmi (1817 – 1881) from the Greek, *ptoma,* meaning something that has fallen down, a corpse, and now, poisonous.

The Greek prefix, *pteris-,* defines the botanical world of the ferns or related plants. And thus, pteridology becomes the study of ferns.

Ptosis is a medical term describing the prolapse or sagging of an organ or anatomic structure, typically the eyelids. Its meaning is derived from the older sense of the root, *pt-* , a falling down or dying.

Ptyalin, an amylase found in saliva, derives directly from the Greek *ptyalos*, meaning saliva and descends through Latin, Gothic and Old English to give birth to words such as spew and spittle.

The *pt-* combination emerges also in forming the family name of the Greco-Egyptian kings, the Ptolemies, a word derived from the Greek *ptolemos*, meaning war-like. The origin of the name, Ptah, the arch-diety of the Egyptian cosmogony, is obscure.

In the more archaic languages preceding Greek, the Indo-European tongues, the *pt-* combination tends to be separated and appears as *pet-*. Over the succeeding millennia, the intervening *e-* has disappeared.

– Stanley M. Aronson, MD

Rhode Island Department of Health
Michael Fine, MD
Director of Health

Vital Statistics

Edited by Colleen Fontana, State Registrar

Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	November 2010	12 Months Ending with November 2010		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	194	2,241	212.8	3,002.0
Malignant Neoplasms	204	2,302	218.6	6,044.0
Cerebrovascular Diseases	43	455	43.2	714.5
Injuries (Accidents/Suicide/Homicide)	58	619	58.8	9,988.5
COPD	40	508	48.2	535.0

Vital Events	Reporting Period		
	May 2011	12 Months Ending with May 2011	
	Number	Number	Rates
Live Births	1,005	11,747	11.2*
Deaths	810	10,001	9.5*
Infant Deaths	(9)	(72)	6.1#
Neonatal Deaths	(7)	(70)	6.0#
Marriages	550	6,118	5.8*
Divorces	264	3,308	3.1*
Induced Terminations	360	4,084	347.7#
Spontaneous Fetal Deaths	64	648	55.2#
Under 20 weeks gestation	(50)	(568)	56.8#
20+ weeks gestation	(14)	(78)	6.6#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,053,209. (www.census.gov)

(c) Years of Potential Life Lost (YPLL).

Note: *Totals represent vital events that occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population
\# Rates per 1,000 live births

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Ninety Years Ago, November, 1921

Frederic J. Farnell, MD, make general remarks on endocrine disorders and their relation to the individual in a paper presented before the Rhode Island Medical Society in September of that year. He opens by noting that "the physiologist can scarcely escape the feeling that here he has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism are become foolishness, where fact and hypothesis are habitually confounded and 'nothing is but what is not.'"

Harold I. Gosline, MD, a pathologist for the State Hospital for Mental Diseases in Howard, RI, examines a study made on syphilis in mental cases. He starts by suggesting that possibly not all of the cases of syphilis among patients are valid, and he goes on to discuss various treatments, tests, and mortality reports. Gosline stresses, in the end, the importance of performing a lumbar puncture prior to any discharge, and the yearly testing of blood.

An editorial on chiropractics opens with: "It comes within the range of possible conjecture that the science [sic] of chiropractics has some helpful use, either mental or physical—probably the first—upon the health of some people of certain temperament. It is beginning to be apparent, however, that the 'Reign of Reason' is gaining the ascendency over the 'Rain of Dollars,' heretofore enjoyed by this particular cult, and that their star of popularity is on the wane."

The book *Diseases of Children* by Herman B. Sheffield, MD, is reviewed making note that the author has included all of the recent advances in medical research and disease prevention. There is criticism, however, in that in the author's attempt to fit so much information into a 800-page volume, some information is too brief and may lead to an erroneous impressions.

Fifty Years Ago, November, 1961

A panel presentation on peripheral arterial occlusive disease is presented by Jesse P. Eddy III, MD, Stephen J. Hoye, MD, William P. Corvese, MD, Seebert J. Goldowsky, MD, and Lester J. Vargas, MD. The presentation covers the history and natural course of arteriosclerosis obliterans, prognosis to life and limb, and progression of disease—also noting a correlation between arteriosclerosis obliterans and diabetes and age. From there, the topics move to arterial occlusions, diagnoses, arteriography, and surgical treatments including endarterectomy, graft, and lumbar sympathectomy. The presentation finishes with a question-and-answer session moderated by Dr. Eddy.

Robert L.Curran, MD, and Thomas Forsythe, MD, examine an unusual cause of gastrointestinal hemorrhage—systemic neurofibromatosis with involvement of the duodenum. Their case focuses on a 56-year old white female with a three-day history of melena associated with light-headedness and dyspnea. After numerous tests and examinations, on the tenth day a sigmoidoscopy and hemorrhoidectomy were performed. After a couple of more visits due to a reappearance of melena, a laparotomy revealed a tumor consistent with leiomyoma, but a closer examination of the removed tumor turned out to be neurofibromata, a rare finding in the gastrointestinal tract. The patient's convalescence was uneventful and the seven-month follow-up was positive.

An editorial notes: "A computer center at Brown University and increasing references to computers in medical science signal the advent of computers in clinical practice. What a computer can and cannot do is not generally understood." The writer goes on to predict, with anticipation, uses of computers in diagnostics and analysis.

As the Rhode Island Medical Society approaches its sesquicentennial year, its place within the history of state medical societies is examined, placing it eighth oldest (1812) following New York (1807) with the oldest state medical society being New Jersey (1766).

Twenty-five Years Ago, November, 1986

This issue opens with a tribute by Wendy Smith and Stanley M. Aronson, MD, to Seebert J.Goldowsky, MD, who is celebrating his twenty-sixth anniversary as Editor-in-Chief of the *Rhode Island Medical Journal*. The tribute covers his years of schooling, to his long surgery practice and other positions. The tribute also talks about Dr. Goldowsky's father, the first Jewish detective in Rhode Island, and Dr.Goldowsky's history with the journal, and his contributions to the advancement of the medical profession.

The opening article is a surprising discussion on images and use of medicine in the work of James Joyce by Irving A. Beck, MD. Dr. Beck looks at Joyce's early life, literary career, and *Ulysses* in particular, discussing medical allusions, symbols, references, and so forth. A look at Joyce's medical history is also made, drawing some connections between the Irish author's afflictions and some of his writing.

Helen E. DeJong presents an amazing tour of the library of the Rhode Island Medical Society. She notes the society's oldest volume is Pliny's *Historia Naturalis* (1501). Other notable books dating in the sixteenth century include Oribasius's *Collectorum Medicanalium* (1555), Lycosthnes's *Progidiorum ac Ostentorum Chronicon* (1557), and Gorraeus's *Definitorium Medicarum* (1564). The rest of DeJong's roster reads like a fevered wish list of anyone with a fascination for the history of medical sciences.

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