Core Entrustable Professional Activities in Clinical Pharmacology for Entering Residency: Biologics

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Abstract

Biologicals are a rapidly expanding class of medications used in the treatment of many different conditions. This article reviews the common characteristics of this class and the requirements for safe and effective use in patients. Several vignettes are included to illustrate common challenges.

Keywords

entrustable professional activities (EPAs) in clinical pharmacology, medical education, UME, GME, prescribing practices, biologics, proteins, antibodies

The Association of American Medical Colleges has identified critical knowledge and skills that medical students must acquire before graduating to be prepared to function independently at the beginning of their residency training. These are called entrustable professional activities (EPAs) and include the ability to appropriately prescribe medications. The American College of Clinical Pharmacology is providing a set of standards representing the EPAs in clinical pharmacology, which are published as a series of papers in the *Journal of Clinical Pharmacology* under the educational banner "Pearls for Clinical Practice." We have identified the following core topics that every prescribing clinician needs to master:[1] (1) basic pharmacokinetics and pharmacodynamics;[2] (2) dosage adjustment for organ impairment and age;[3] (3) drug–drug interactions; (4) biologics; (5) adherence;[4] (6) identifying, understanding, and interpreting drug information sources; (7) summarizing common problem drugs; and (8) how to work within the health care–providing team. Each topic contains a succinct analytical review of key concepts and is accompanied by several memorable real-world vignettes, followed by a discussion, including a well-reasoned solution. The target audience includes medical students and residents, medical educators, and faculty at academic medical centers. It also is designed to serve as a refresher for practitioners and other medical professionals.

In this article, we illustrate how understanding the basics of human immunology and clinical pharmacology informs the selection of an optimal treatment strategy using biologics. Biologics belong to a special class of drugs defined by the Food and Drug Administration and include "viruses, therapeutic sera, toxins, antitoxins, vaccines, blood, blood components or derivatives, allergenic products, or analogous products that are applicable to the prevention, treatment, or cure of a disease or condition of human beings" (CFR 351 of the Public Health Service Act). Although hormones such as insulin, glucagon, and human growth hormone are regulated separately under the Food, Drug, and Cosmetic Act, some of these agents will be considered in this article because they share many properties with biologics.

After reading this article, the reader will be aware of the common characteristics of this class of medications and the requirements for safe and effective use in patients. High cost may require preauthorization of payment and may require patients go to a

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specialty pharmacy to obtain these medications. Almost all biologics require parenteral administration, and so patients and their caregivers may require education on reconstitution and injection or infusion techniques. Alternatively, arrangements may be made for administration at an infusion center. Some biologics require special cold storage, but strict avoidance of subfreezing temperatures. Class-specific adverse reactions that may be anticipated include immunological responses requiring pretreatment or loss of response because of the development of antidrug antibodies (ADAs).

Common Characteristics of Biologics

There has been a long tradition of use of medications derived from human or other mammalian sources. Aside from blood products and vaccines, many of these medications are defined proteins. With the advent of recombinant gene technology, most protein-based therapeutics are produced in genetically modified microorganisms or cell lines. This class of therapeutic proteins is usually referred to as "biologics" in clinical pharmacotherapy. The class includes monoclonal antibodies, antibody–drug conjugates, peptibodies (peptide–Fc fusion products), cytokines, and growth factors, among others.

The application of recombinant technology has allowed the manufacture of humanized proteins that improve the safety of biologic therapy and allow a more stable drug supply. The risk of antigenic responses associated with administration of nonhuman proteins is reduced with humanized proteins. Therapeutic products derived from human donors carry the risk of infectious disease transmission. In addition, recombinant technology enabled the development of complex polypeptides and proteins that are not naturally occurring but are able to exert potent and highly specific effects against disease conditions. The past 3 decades have seen exponential growth in the development of these engineered biologics. Although human insulin was the first therapeutic protein produced with recombinant technology, in 1982, larger, more complex molecules, such as monoclonal antibodies with high specificity for defined molecular targets are now widely used biologics for many indications. Fusion proteins and chemically modified proteins combine humanized versions of replacement proteins, such as coagulation factors or growth hormones, with other structures such as polyethylene glycol, human serum albumin, and carboxy-terminal peptides. These modifications allow modulation of the pharmacologic properties of the active components, for example, to delay elimination and allow for longer dose intervals.[5]

Biologics are used to treat diseases in every medical specialty. Traditional aspects of pharmacokinetics, such as absorption, distribution, metabolism, and excretion and half-life, cannot be generalized across biologics because of their highly individualized nature. The mechanisms of action include agonism (eg, binding to a cellular target to trigger a desired function) and antagonism (eg, binding to and blocking a normal cellular receptor or disabling or competing with the action of natural ligands). Alternatively, they may replace or supplement endogenous proteins with enzyme, hormone, or growth factor activity. Their binding to target molecules is often exquisitely specific, but the specificity of the clinical response depends on the target's distribution within the body. Undesired on-target effects or toxicities may be encountered when the target is expressed in different cell types other than the therapeutic target tissue.[6] In addition, the physiologic action of biologics is tightly regulated, especially if they have hormone or growth factor activity, and they may act locally rather than systemically. Examples of widely used biologics with hormone or growth factor activity are erythropoietin (stimulating the production of circulating red blood cells by the bone marrow), insulin (regulating blood sugar), human growth hormone, granulocyte colony-stimulating factor, and bone morphogenetic protein for fracture wound healing.

Given that many biological agents are antibodies or antibody-like structures that bind to a specific epitope on the corresponding target molecule, more than one drug can be used to target the same pathway. One such example is the anti–tumor necrosis factor (TNF) pathway and the drugs targeting it (ie, infliximab, etanercept, and their biosimilars). Infliximab is a chimeric (human and murine components) monoclonal antibody biologic drug that works against TNF-α by binding directly to it and preventing its interaction with TNF receptor (TNFR). Etanercept is a recombinant human protein composed of the ligand-binding portion of TNFR fused to the Fc portion of immunoglobulin IgG1, which serves as a decoy receptor for TNF-α. Both drugs are used to treat autoimmune diseases such as rheumatoid arthritis and can be used interchangeably, but do not have the same mechanism of action, dosage, route of administration, or toxicity profile. This adds to the complexity of an already difficult and often confusing armamentarium of biologics.

Common characteristics of biologics are their need for parenteral administration; care in storage, as some products need to be refrigerated; high cost associated with their recombinant production; and adverse reactions caused by immunogenicity. Immunogenicity refers to eliciting an immune response against the therapeutic protein by breaking the B-cell tolerance usually present for endogenous proteins. Although the

incidence of ADA formation is usually lower for humanized biologics compared with animal proteins, even fully human biologics may elicit ADA formation. There is large variability with regard to the incidence and impact of ADA formation among different biologics, and factors such as previous treatment with similar biologics, route of administration, duration of therapy, dose, and genetic predisposition further increase the variability in immunogenicity reactions. However, not all ADAs affect the efficacy and/or safety of the biologic: the titer (ie, amount), binding affinity, and ability to neutralize the biologic's activity also determine whether ADA formation is detrimental to therapy with the affected biologic. Humanized biologics have a low incidence of antidrug antibodies, and most do not neutralize the activity of the drug.[7,8] The incidence reporting for immunogenicity is highly variable and dependent on the assay measuring the antidrug–antibody. There is no standard unit of quantification, and thus the ADA determinations are highly dependent on the assay. Further, ADA assays cannot and should not be compared between different products and assays.[9] Even for adalimumab, the first fully human monoclonal antibody, immunogenicity rates were initially reported as 1% with methotrexate coadministration and 10% as monotherapy. Today, after much scrutiny for adalimumab during biosimilar development activities by many different companies, it is now well recognized that 60%–70% of individuals develop ADAs.[10] Further, even nonneutralizing activity of ADAs can cause increased clearance and thus reduced exposure and efficacy.[9]

Biologics also share many pharmacokinetic characteristics.[11,12] If administered by subcutaneous injection, they are absorbed into the lymphatic system, from which they slowly enter systemic circulation, resulting in a delayed onset of action. Because of their large molecular size, they are largely confined to the vascular space, with substantially lower exposure in the interstitial space of peripheral tissues. They are removed by enzymatic cleavage by proteases and peptidases, tissue-receptor-mediated mechanisms, in the case of IgA-based antibody biliary secretion and by renal metabolism in the case of small proteins (<70 KDa).[13]

The pharmacokinetics and pharmacodynamics of biologics can be modified by other drugs, and conversely, the activity of concomitantly administered drugs can be significantly altered by biologics, particularly cytokines and cytokine modulators.[14] This is especially of concern for drugs that have a narrow therapeutic window. Today's clinicians require a firm grounding in the mechanisms of action of biologics, so that drug–drug interactions can be anticipated and adverse reactions avoided or mitigated.

Adverse reactions that may be anticipated include allergic reactions requiring pretreatment (diphenhydramine, acetaminophen) and loss of therapeutic response because of the development of ADAs that lead to undesirable ADA-mediated immunotoxicity.[15] ADAs against biologics can alter absorption, distribution, metabolism, and excretion, thereby greatly confounding the interpretation of pharmacokinetic/pharmacodynamic assessments. Antagonistic antibodies targeting immune checkpoint receptors or ligands or agonistic antibodies targeting immune costimulatory receptors can overstimulate the immune system. This can unmask autoimmune responses such as inflammatory thyroiditis followed by hypothyroidism, sudden type I diabetes, and other treatment-associated autoimmune sequelae, some of which are life-threatening. Outside of patient immune status and exposure history, we cannot predict which patient may have an increased risk of adverse immune response. To ensure that patients receive safe and effective treatments, clinicians must be vigilant for the appearance of autoimmune side effects, loss of drug activity, and atypical symptoms of infection or other conditions in patients receiving immunosuppressive biologics.

Monoclonal Antibodies

One of the most versatile and widely used groups of biologics is the class of therapeutic monoclonal antibodies and antibody-derived proteins. They can be engineered to act as agonists, antagonists, and effector molecules or used to direct radio- or pharmacologic agents to specific cellular targets, either in the configuration of native immunoglobulins or modified scaffolds, such as bispecific antibodies, fusion proteins, antibody fragments, and antibody–drug conjugates.[16] Bispecifics are antibody derivatives with the ability to bind to 2 or more targets, for example, to engage immune cells in activity against tumor cells by bridging cell-type-specific surface proteins.[17] Antibody–drug conjugates are combinations of potent small molecules with an antibody as a targeting agent for a specific cell type.[18]

Monoclonal antibodies are now important components of the treatment of a wide range of specialties including oncology, rheumatology, transplantation, pulmonology, and regenerative medicine.[19] Because of their target specificity and limited off-target toxicity, monoclonal antibodies are usually safe drugs and are the most rapidly expanding class of drugs in oncology, in which the therapeutic index (safety versus efficacy) of commonly used chemotherapeutics is low.[20]

The half-life of monoclonal IgG antibodies is similar to that of normal immunoglobulin, usually ranging from 21 to 24 days. This is a very long half-life

compared with most small-molecule therapeutics.[21] After repeated administration, particularly under long-term therapy, some patients mount a natural antibody-mediated immune response to the therapeutic monoclonal antibody. Such antidrug antibody formation often results in more rapid clearance on administration of additional courses of therapy, potentially resulting in therapeutic failure.[22] Companion diagnostics are becoming more important for the identification of patients who will benefit from the specific monoclonal antibody treatment and are also useful for measuring the plasma concentration of therapeutic antibodies and detecting the emergence of antidrug antibodies.

Discussion

Contemporary drug therapy using biologics has allowed exquisitely targeted therapy and is advancing at an exponential pace. Using this class of drugs, very precise functions may be targeted, often mimicking the body's natural processes, providing specific relief to patient's symptoms. However, there are some disadvantages of these therapies. Biologics require parenteral administration, and so patients must be educated on self-administration or rely on visiting nurses or trips to an infusion center. Biologics may be expensive and require special authorization from health insurance for coverage or distribution through specialty pharmacies. Biologic therapies may lose their effectiveness because of the development of antidrug antibodies or neutralizing antibodies that increase clearance of the drug or interfere with binding to the receptor.

In summary, today's clinicians require a firm grounding in the accessibility challenges as well as the mechanisms of action of biologics, so that their patients can be sure of a steady supply and that the medications may be administered appropriately and adverse reactions are avoided or mitigated early. The clinical vignettes provided in the appendix illustrate some of the unique challenges of using biologics as part of the therapeutic armamentarium for the treatment of chronic diseases.

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Declaration of Conflicting Interests

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Appendix: Clinical Vignettes

Infliximab ADA and Rheumatoid Arthritis

Mrs. J., a 44-year-old woman, was diagnosed with rheumatoid arthritis 2 years ago. After 3 months of prednisone 10 mg per day and hydroxychloroquine 400 mg per day, she still showed symptoms of active disease, and so infliximab was added to her regimen. It was administered by intravenous infusion every 4 weeks at a dose of 8 mg/kg.

Six months ago, at her last clinic visit, Mrs. J. showed signs of only minimal disease. She could conduct most activities without difficulty or pain. At this clinic visit, she reports increasing difficulty in dressing herself, especially fastening buttons. It is hard to get in and out of bed and in and out of her car. She needs assistance moving heavy objects above her head and finds walking outdoors, even on flat ground, painful. When assessed all together, her patient activity score has gone from 3.5 (low disease activity) to 7 (moderate disease activity). There is also laboratory evidence that her disease has worsened. Her C-reactive protein has increased to 41 mg/L. Previously, her infliximab trough level was 18.3 mg/mL, but it is now below the limit of quantification (<0.03 mg/mL), and antidrug antibody levels that were previously below the limit of quantification (<12 AU/mL) have increased to 260 AU/mL. The decision is made to switch to a different medication.

Infliximab ADA Commentary. Infliximab is a mouse–human chimeric IgG1 antibody that is indicated for the treatment of rheumatoid arthritis as well as several other inflammatory conditions. The incidence of ADAs to infliximab in patients was approximately 10%, as assessed 1 to 2 years after starting therapy.[23]

Although the development of ADAs against infliximab may not result in loss of clinical response for a specific patient, the presence of ADAs is associated with lower drug concentrations, decreased efficacy, and

increased frequency of adverse events such as infusion reactions.[24] The detection of ADAs is important in this case, as it helps to explain the loss of clinical response for Mrs. J. Some assays that are used to detect ADAs may report false-negatives because of the interference of infliximab in circulation, and so it is important to collect samples for ADA testing at times of anticipated trough concentrations or after medication has been discontinued and permitted to wash out.[22]

There are several factors that may influence the development of ADAs to infliximab. Patients who have had ADAs against their first anti-TNF therapy are at increased risk of developing ADAs against a second anti-TNF agent.[24] The treatment regimen may influence the development of ADAs. Higher doses, continued dosing to tolerance, and coadministration with methotrexate, azathioprine, mercaptopurine, or hydrocortisone may decrease the incidence of ADAs or overcome their presence.[24] Biologic agents all carry some risk of the development of ADAs, and so clinicians need to keep this in mind when patients appear to have lost response to previously effective therapy.

Etanercept and Global Immune Suppression

Mr. M. is a 53-year-old man with a long history of rheumatoid arthritis requiring bilateral total hip and knee replacements. His surgical procedures were complicated by septic arthritis requiring several revisions. He has been treated with different treatment modalities, but over the last 2 years he has been stable with etanercept, a TNF inhibitor, administered subcutaneously 50 mg once weekly. He also had a history of hypertension that was well controlled on atenolol. The patient did not have any medication allergies. He did not use tobacco, alcohol, or street drugs. He lived alone and was independent, and his family history was positive for rheumatoid arthritis in his mother.

The patient was nonambulatory when he presented to the emergency room by ambulance after 2 days of generalized weakness, urinary frequency, and severe left flank and left thigh pain. The patient also reported nausea, emesis, and foul-smelling, cloudy urine. On initial evaluation the patient was found to be hypothermic to 34.5°C, tachycardic (heart rate, HR, 124 bpm) with a regular heart rhythm and no abnormal sounds, and hypotensive (blood pressure, 88/43 mm Hg). He was pale, diaphoretic, and in moderate distress because of the pain. He had left basilar crackles on lung auscultation and a soft, nondistended, and nontender abdomen with normal bowel sounds. He had severe left and mild right costovertebral angle tenderness on percussion and no significant suprapubic tenderness. He had limited range of motion of his cervical spine and shoulders bilaterally, which was reported to be chronic and unchanged. The patient had full range of motion bilaterally of his hips and knees without significant stiffness or tenderness, but severe tenderness on palpation over the left medial thigh. No skin changes or edema could be appreciated in the area of tenderness. His laboratory workup was unremarkable, including white blood cell count 9100/μL, with 78% neutrophils and 19% lymphocytes. Urine analysis was positive for white blood cells, red blood cells, bacteria, and nitrates. A computerized tomography (CT) scan of the abdomen and pelvis was performed and revealed numerous bilateral kidney stones, with a large 18 $\times$ 9 mm staghorn calculus in the left renal pelvis. The patient also had bilateral perinephric tissue stranding, indicative of pyelonephritis. At this point the patient required resuscitation with intravenous fluids. His blood pressure improved after 2 L of normal saline. He was started on the intravenous antibiotic piperacillin–tazobactam for complicated pyelonephritis, and urology was consulted. Once he was hemodynamically stable, he underwent left urethral stent placement. Urine and blood cultures were sent for further analysis.

Forty-eight hours postprocedure, the patient continued to be hypotensive, tachycardic, diaphoretic, and hypothermic. His antibiotic regimen was escalated, and vancomycin 1 g every 24 hours was added. The patient's urine and blood cultures came back positive for *Proteus mirabilis*, pansensitive. The patient reported improvement of the left flank pain, but his left thigh pain was unchanged and severe. Orthopedic surgery was consulted. Left hip and knee radiographs were unremarkable without signs of infection or hardware malfunction. Magnetic resonance imaging of the left hip and thigh was performed as well and revealed cellulitis of the left medial thigh, despite the absence of edema or erythema in the affected area on repeated physical examination.

After a full 72 hours of the antibiotic regimen, the patient demonstrated some improvement, and his vital signs stabilized. A repeat blood culture was negative. The patient continued to improve and was discharged on oral antibiotics.

Etanercept Case Commentary. TNF together with IL-6 and IL-1 is a major proinflammatory cytokine of the innate immune system. These cytokines are also called "early responders" because they are produced early in the infectious process. TNF, IL-1, and IL-6 have systemic effects that contribute to host defense and are responsible for many of the clinical manifestations of infection, for example, fever, malaise, loss of appetite, and elevated white blood cell count.

TNF binds to 2 different types of receptors, TNF-RI and TNF -RII, which are present on most cell types. Etanercept is a soluble tumor necrosis factor

(TNF) receptor. This is a fusion protein consisting of the extracellular ligand-binding portion of the human tumor necrosis factor receptor linked to the Fc portion of human IgG1. It binds specifically to TNF and blocks its interaction with cell-surface TNF receptors, thereby downmodulating the biological responses induced or regulated by TNF.

In Mr. M.'s case we can see the rapid progression of the clinical condition from the initial infection 2 days prior to presentation to early sepsis.[25] Mr. M. did not exhibit many of the classical "warning" sings of an ongoing infection (eg, fever, elevated white blood cell count, edema, or erythema in the area of cellulitis). Also, his response to antibiotic therapy was delayed, and his condition continued to deteriorate despite appropriate treatment. TNF plays a key role in recruiting and mobilizing neutrophils to the site of infection. Neutrophils have phagocytic activity, as well as playing a pivotal role in activating adaptive immune responses. By attracting neutrophils to the site of the infection TNF facilitates the clearing of pathogens and the infectious process. Furthermore, TNF acts to increase prostaglandin production in the hypothalamic cells, causing hypothalamic thermoregulatory center modulation, resulting in elevated body temperature–fever.[25]

Despite the suppression of TNF, Mr. M. displayed several symptoms that are typically associated with TNF activity (eg, malaise, appetite loss, peripheral vasodilation causing hypotension). Although TNF was inhibited, IL-1 and IL-6 responses were intact. These cytokines have distinct structures, receptors, and molecular mechanisms of action, but their biological activities significantly overlap with TNF. Thus, septic patients on etanercept therapy may present with atypical symptoms.

As different as the outcomes were, the 2 anti-TNF vignettes described above could apply to any of the several biologics targeting the TNF pathway. Every clinician must be continually vigilant for loss of activity because of ADAs or, at the other extreme, overstimulation or oversuppression of the immune system. The availability of multiple agents targeting the same pathway provides the opportunity to manage these adverse effects, as ADAs to one drug will likely not interfere with another biologic, as the ADAs do not cross-react. Unfortunately, patients who develop ADAs to one biologic may be at risk to develop ADAs to other ones, as is the case for patients with rheumatoid arthritis who are treated with anti-TNF agents.[24]

Biologics with different generic names may target the same pathway or even the same molecule; for example, recombinant factor VIII. As more of these drugs become available from different manufacturers, clinicians will need to recognize that some biologics targeting the same molecule are actually biosimilars, that is, biological products with no clinically meaningful differences in terms of safety, purity, and potency,[26] whereas others have differences in molecular structure, potency, and pharmacokinetic parameters.

Pembrolizumab and Thyroid Dysfunction

Mrs. S. is a 62-year-old woman with a medical history of hypertension well controlled on hydrochlorothiazide, type II diabetes controlled on metformin, and a recent diagnosis of stage IV adenocarcinoma of the lung. She was in her usual state of heath until 6 months ago, when she developed a recurrent productive cough with evidence of scant hemoptysis. She subsequently developed worsening dyspnea on exertion as well as a fever. Her primary care doctor obtained a chest x-ray, which revealed a right middle lobe pneumonia, and she was treated with a fluoroquinolone, with resolution of her fever and modest improvement of her dyspnea.

Two months later, she again developed fever, chills, and a cough productive of green sputum with hemoptysis. She was admitted to the hospital for a recurrent right middle lobe pneumonia, and a CT of her chest revealed a 6-cm right middle lobe mass, a moderate right-sided pleural effusion, bilateral bulking mediastinal lymph nodes, and scattered subcentimeter pleural-based nodules in both lungs. A subsequent positron emission tomography (PET)-CT revealed PET uptake in the above lesions as well as in a 2-cm liver lesion and right iliac crest lesion. A liver biopsy confirmed metastatic adenocarcinoma of the lung, with only a *KRAS* mutation detected on molecular testing and program death ligand–1 (PDL-1) IHC-positive stain in 60% of the tumor cells.

Mrs. S. was seen by a medical oncologist and was in good spirits despite her recent diagnosis and stated she was willing to do whatever is necessary to "fight her cancer." Of note, she was still able to do her activities of daily living, although she did get short of breath after walking 2 blocks and had lost 20 pounds over the last 2 months. After discussing the potential autoimmune sequelae associated with anti-program death–1 (PD-1) inhibitors, she was started on the anti-PD-1 inhibitor pembrolizumab.

She returned in 3 weeks for her second treatment and stated that her breathing had significantly improved and that she had "never felt so energetic." She went on to explain that she had had some trouble sleeping, which made her more irritable. She was also surprised that despite eating more than she had for the last 6 months, she had actually lost 4 pounds. Of note, on examination her heart rate was 105 bpm with a blood pressure of 120/65 mm Hg and an oxygen saturation

of 96%, improved from 91%. She was administered her second dose of pembrolizumab and told to follow up in 3 weeks for a physical examination, phlebotomy, and her third treatment.

Two days later, Mrs. S. awoke with crushing chest pain and felt like "her heart was beating outside her chest." She was brought to the emergency room, where an electrocardiogram revealed supraventricular tachycardia at 150 bpm, with upright p waves present in lead II. She was administered adenosine and converted to a sinus tachycardia at 105 bpm. Her laboratory values were significant for a troponin of 0.1 ng/mL and a thyroid-stimulating hormone (TSH) of 0.01 mIU/L and free thyroxine (T4) of 2.50 μg/dL. During her admission, she was stabilized and started on metoprolol T4 and her heart rate was 82 bpm in sinus rhythm at discharge.

She followed up in clinic for her 3-week appointment and stated that she was feeling better and able to sleep at night. Her pulse was strong and regular at 75 bpm. Her labs were drawn, and her TSH was now in the normal range at 0.75 mIU/L, and her free T4 was in the high normal range at 1.6 μg/dL. She was administered her third treatment and instructed to return in 3 weeks for her next cycle and restaging scans.

At her next visit, the patient stated that her "breathing is the best it has been in 2 years!" but she was disappointed that her energy level was "worse than ever." She was relieved that she has gained 10 pounds in the last 3 weeks but wondered if this "extra weight" was slowing her down. Of note, her examination was significant for a resting pulse of 51. Her restaging scan demonstrated a 50% reduction in her lung and liver lesions and complete resolution of her pleural effusion. She was overjoyed that her treatment was working but worried that her quality of life seemed to be getting worse.

Her oncologist ordered repeat thyroid studies and found that her TSH was now 35 mIU/L and free T4 was 0.15 μg/dL. Mrs. S. was subsequently started on a replacement dose of levothyroxine, which was titrated over a number of weeks until her TSH and free T4 were in the normal range and Mrs. S.'s symptoms resolved.

Pembrolizumab Case Commentary. Mrs. S.'s story illustrates the need to be vigilant for possible autoimmune side effects of the currently available checkpoint inhibitors including anti-CTL4 and anti-PD-1/PDL-1 inhibitors.[27,28] Because of their high specificity, monoclonal antibodies such as pembrolizumab usually do not have relevant off-target toxicity, but can exhibit substantial on-target toxicity. In the discussed case, immune system stimulation by pembrolizumab therapy resulted in thyroiditis and subsequent thyroid dysfunction. Checkpoint inhibitor–mediated thyroid dysfunction occurs in approximately 9% of patients with solid malignancies, and the rate is even higher in patients who receive anti-CTL4 inhibitors.[29] Although patients are at increased risk for both hyperthyroidism and hypothyroidism compared with nonimmunotherapy cancer agents, the majority of cases will eventually result in irreversible hypothyroidism.[27,28] Similar issues with thyroid dysfunction have been observed in a number of solid malignancies, most notably melanoma. Other autoimmune sequelae have been associated with systemic administration of immune checkpoint inhibitors.

In this case, Mrs. S. developed a classic inflammatory thyroiditis, which is characterized by a rapid onset after treatment (median onset, 3 weeks), with the common symptoms of tachycardia, weight loss, insomnolence, irritability, and concurrent depressed or absent TSH and elevated free T4.[27,28] These patients often require beta-blocker therapy to keep the heart rate below 80 bpm but rarely require additional therapies such as antithyroid drugs (thionamides), radioiodine, or surgery.[28] In the majority of cases, this initial period of hyperthyroidism is followed within 3 to 6 weeks by hypothyroidism. These patients will now require discontinuation of their beta-blocker therapy and appropriate thyroid replacement therapy with levothyroxine. It is therefore standard of care to obtain serum TSH levels at 3- to 6-week intervals while the patient is on treatment and periodically after treatment is completed. Once a diagnosis of hyperthyroidism is established, it is essential to follow the patient closely for signs of symptomatic hyperthyroidism and conversely over the next 3 to 6 weeks for signs of hypothyroidism.

Bevacizumab and Wound Complications

Mr. S. is a 60-year-old man with metastatic adenocarcinoma of the right colon with lung and liver metastases. He had previous abdominal surgeries remotely (right hemicolectomy for stage III colon cancer and cholecystectomy/appendectomy for benign disease). He has been treated with second-line 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab intravenously every 2 weeks. His most recent CT scans earlier this year showed modest reduction in tumor burden.

While visiting family out of town, he presented to the hospital with complaints of abdominal pain. Abdominal x-ray and CT scan showed known liver metastasis but new partial small bowel obstruction. Conservative measures with bowel rest and intravenous hydration were initially tried. He had progressive symptoms, and he was urgently taken to the operating room for exploratory laparotomy. Intraoperatively, there was no evidence of carcinomatosis, but extensive abdominal adhesions were noted. Lysis of adhesions and release

of small bowel obstruction was performed by general surgery.

Approximately 2 weeks postoperatively, he was found to have wound dehiscence and infection requiring antibiotic therapy and extensive wound care, all possibly associated with bevacizumab treatment.

Bevacizumab Case Commentary. Bevacizumab is a humanized monoclonal antibody targeting vascular endothelial growth factors and is approved for use in several malignancies including colorectal cancer, non–small cell lung cancer, and renal cell carcinoma. Adverse reactions include infusional/hypersensitivity reactions, hypertension, thromboembolism, and proteinuria (Avastin [bevacizumab] prescribing information; South San Francisco, California: Genentech Inc.; December 2016.).[30] Bevacizumab has been associated with wound dehiscence, wound infection, and gastrointestinal perforation. The current recommendation is to wait at least 6 weeks after surgery prior to initiating or reinitiating bevacizumab, but the optimal interval between bevacizumab and surgery has not been determined. Surgical complications including fatal events are increased in patients who have received bevacizumab.

In Mr. S.'s case, the surgery was urgent. Further, the surgeon may have not been aware of the recent administration of bevacizumab. The Mr. S. case illustrates that for patients receiving bevacizumab or any antiangiogenic agents, bleeding and wound complications are common, and therefore it may be advisable to wait at least 6 weeks after bevacizumab before elective major surgical procedures are performed.[30,31] Further, the clinician administering bevacizumab should always emphasize to patients the risks of bleeding and wound complications, especially the patients who might be undergoing surgical procedures.[31]

Growth Hormone and Injection-Site Reactions

Master J. is a 6-year-old boy who has been assessed for short stature. He is the second child in his family and weighed 3.2 kg at birth, after a normal pregnancy and delivery. He is current on his immunizations and has enjoyed good health, but is much smaller than all of his kindergarten classmates. His growth has always been slow, and he has grown only 3 cm over the past year. He is now 102 cm tall (<3rd percentile for height) and weighs 16 kg (10th percentile for weight). Further investigation has shown that he has low serum growth hormone that is unresponsive to stimulation and below normal insulin-like growth factor (IGF-1) of 35 μg/L. The decision has been made to start growth hormone replacement therapy,[32,33] and he and his mother have come to receive training on dose preparation and administration. Although he will learn how to inject his medication later, his mother will take responsibility for now. The nurse practitioner explains that there will be ongoing monitoring of his glucose metabolism (insulin, HbA_{1c}, fasting glucose), and other hormones (TSH, free T4, free T3, and cortisol) because sometimes growth hormone therapy may uncover other deficiencies.[33]

Master J. and his mother return to the clinic regularly over the next year. At their first visit, they note various red spots that are injection-site reactions. Master J. reports that pain was less severe when injections were given to his arms, and so most injections are given in that location, but recently, even that location hurts. The mother was instructed that all injections be rotated among 4 sites in the upper extremities, 2 locations in each arm. Just prior to the second visit, they ran out of medication because of problems with prescription coverage and the high cost of medication. The office staff asked Master J.'s mother to provide the necessary documentation to her insurance so that coverage was renewed. By their next visit, injection sites looked good, Master J. showed a calendar to the nurse with stickers showing how they rotated sites, and his IGF-1 normalized to 105 μg/L. At a subsequent visit, Master J. had grown, and so his dose was adjusted to 0.5 mg daily and at his 1-year visit, he had grown 12 cm and was 114 cm tall (between 3rd and 10th percentiles).

Growth Hormone Commentary. Growth hormone replacement, as is true for all biologics, is not absorbed after oral administration and must be administered by subcutaneous injection. Patients or their caretakers must be trained on proper storage, dosage preparation, and administration techniques. Biologics can be very expensive and may require special authorization for coverage and specialty pharmacy dispensing. Patients may discontinue or significantly modify prescribed regimens if they have difficulty obtaining the drug, have painful reactions at the site of administration, or do not perceive an immediate benefit.[4] Injection-site reactions occur with many biologics. Patients must be counseled what they are and when they might signal something more important, but should also be advised that injection-site rotation is often enough to avoid inflammation.[34]

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