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RESEARCH ARTICLE

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Therapeutic monoclonal antibodies and clinical laboratory tests: When, why, and what is expected?

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Background: We herein provide an overview of the clinical laboratory tests that should be performed before, during and after using therapeutic monoclonal antibodies (mAbs) and the clinical laboratory tests that may be affected by mAbs.

Methods: The labels of FDA-approved therapeutic mAbs were downloaded from DailyMed (the official website for drug labels) and were used as the sources of data for this review.

Results: It was found that most of the labels provided information relevant to the clinical laboratory tests, including the tests needed before mAbs treatment to check the patients' background status and to identify potentially sensitive patients, the tests needed during or after the treatment to evaluate the patients' response, and the mAbs that may lead to false positive or negative results for clinical laboratory tests.

Conclusions: The present findings will be of interest to physicians, laboratory scientists, those involved in drug development and surveillance and individuals making health care policy.

KEYWORDS

clinical laboratory tests, FDA labels DailyMed, laboratory test interference, mandatory testing, therapeutic monoclonal antibodies

1 | BACKGROUND

Monoclonal antibodies (mAb) are antibodies that are made by identical immune cells derived from a unique parent B lymphocyte cell.[1] During the past few decades, mAbs have become an integral and widely used technology for both laboratory diagnostics and clinical treatment.[2,3] As it the case for many other prescription drugs, it is necessary to perform clinical laboratory tests before and after the treatment with therapeutic mAb to screen for potentially sensitive patients, check the patients' background health status and to evaluate the response to treatment. It has also been reported that some mAbs may interfere with clinical laboratory tests, especially diagnostic kits that use mAb to detect a specific analyte.[4,5] However, to the best of our knowledge, there have not been any systematic review about the clinical laboratory tests needed for and affected by therapeutic mAb based on the drug labels.

Drug labels provide an excellent source of data for pharmacoepidemiological studies because they contain detailed information about the individual drugs. Therefore, we reviewed and analyzed all the labels of FDA-approved therapeutic mAbs deposited in DailyMed, the official website for FDA-approved drug labels (https://dailymed.nlm.nih.gov/dailymed/index.cfm), to provide a detailed profile of the clinical laboratory tests which should be performed before, during and/or after the treatment with therapeutic mAbs, and information about the mAbs that have the potential to affect clinical laboratory tests.

2 | COLLECTION OF DATA OF FDA-APPROVED MABS

We downloaded PDF labels for all therapeutic mAbs from the DailyMed database (https://dailymed.nlm.nih.gov/dailymed/), which contains nearly all of the labels for US FDA-approved drugs. If there were duplicate labels for the same therapeutic mAb from different manufacturers, or the labels were updated at different times, only the latest label was used for the study. A hyperlink was established to

access the information conveniently, and the findings for each Mab are presented in Table 1.

Stemmed keywords were used to search the label contents for relevant information. These keywords included "analy*", "assay", "clinic*", "determine*", "lab*" and "test" to cover the potentially useful information to the best extent possible. Every stemmed keyword represented several words potentially related to clinical laboratory testing (eg, "analy" was used to find information related to "analyse(d)(s)", "analyze(d)(s)", "analysis", "analyte", and "analytical"). The first two authors of the manuscript, respectively, searched the documents and input the data. When there were differences in the descriptions found between the authors, they discussed the findings with the other authors, and the group's consensus regarding the findings was used for the analysis.

3 | OVERVIEW OF THE FDA-APPROVED MABS

More than 100 therapeutic mAbs have been approved by FDA so far. But there were only 50 therapeutic mAb available on the US market as of May 2016, because the others (i.e., gemtuzumab [20] and efalizumab [21]) had been withdrawn due to a lack of efficacy, adverse reactions, or loss of market share (replaced by other treatments).

The currently marketed therapeutic mAbs are generally used to treat cancer, autoimmune disease (e.g., rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and systemic lupus erythematosus), microbial infections, and rejection. The treatment of cancer is the field with the most therapeutic mAbs, and is also the main direction of development. In total, 20 therapeutic mAbs (>40% of the currently marketed therapeutic mAbs) are being used for the treatment of cancer.

4 | CLINICAL LABORATORY TESTS FOR MABS

The most practical finding of this study was that most of the labels for human therapeutic mAbs provide explicit information related to clinical laboratory testing. Most of the information was about the clinical laboratory tests that need to be performed before treatment and the influence of mAb treatment on the accuracy of clinical laboratory tests.

4.1 | Clinical laboratory tests needed before mAb treatment

Some patients taking therapeutic mAbs may develop side effects, mainly immunotoxicity. One of the aim of performing clinical laboratory tests before mAbs treatment is to avoid this situation. Most of the therapeutic mAbs used to treat autoimmune diseases and rejection target immune system-related molecules located on the surface cell membranes.[22] For example, TNF-α is the target of adalimumab, certolizumab-PEG and infliximab. The targets for basiliximab, canakinumab and ixekizumab are IL-2Rα, IL-1β, and IL-17A, respectively (Table 1). The agents targeting these immune molecules often impair the cells' functions, weakening the patients' immune system. For example, during basiliximab treatment, basiliximab target IL-2Rα, and decreased its protein levels in patients.[23,24] IL-2Rα is the α chain of IL-2 receptor on the surface of certain immune cells. The IL-2 receptor recognizes the signal of IL-2 and initiate immune response. In this way, the decreased IL-2Rα levels would suppress the immune system of patients. Therefore, immunosuppression was often observed in patients taken in basiliximab treatment.[23,24] Due to these effects, the patients taking these agents have a risk for the reactivation of pathogenic microbes in latent infections, such as tuberculosis (TB) and hepatitis B virus (HBV) in patients taking anti-TNF-α mAbs, which may be fatal for the patients. Patients should therefore be tested for latent infections before treatment is initiated. For example, before treatment with adalimumab, it should be determined whether the patient has active or latent/dormant TB. Checking for latent infections prior to drug treatment could, to a large extent, avoid the onset of these diseases induced by the inhibition of immunity. Therefore, tests for active TB and latent infection are needed before adalimumab treatment (Table 1).

For some therapeutic mAbs, especially those used for cancer treatment, screening for potentially sensitive patients is needed to determine whether the drug is expected to have an effect. Trastuzumab, which inhibits HER2-mediated signals that promote tumor growth, is used to treat the patients with HER2-positive breast and gastric cancer. Cancer patients should be screened using FDA-approved diagnostic kits before the treatment to confirm that they express HER2. Such selection limits the treatment to those who should respond to the drug. Therefore, determining whether a mAbs would be effective for a patient is another aim of performing clinical laboratory tests before mAbs treatment.

According to the reasons mentioned above, clinical laboratory tests are need before treatment of more than half of FDA-approved mAb drugs. Accurately, there are 32 mAbs need to perform clinical laboratory tests before their treatment (Table 1).

4.2 | Clinical laboratory tests needed during/after mAb treatment

Laboratory tests monitoring for safety and efficacy in patients is needed for all drugs, and mAbs are no exception. The mAbs are usually better tolerated than small molecules because they are more specific for the target and do not interact with cytochrome P450 or other transport proteins in the body, resulting in a reduced potential for drug/drug interactions. However, while they are generally well tolerated, mAbs may be associated with adverse events (AEs) such as hepatotoxicity, nephrotoxicity, and hematotoxicity. Many AEs are target-related, and will be specific to the antibody target and the therapeutic area of use. Alternatively, mAbs may cause toxicity by interacting with the target antigen on tissues other than the intended tissue. For example, skin toxicity is associated with cetuximab (used to treat colorectal and head and neck cancer), which inhibits the epidermal growth factor receptor

TABLE 1 The FDA-approved therapeutic monoclonal antibodies and clinical laboratory tests

Generic name	Trade name	Target(s)	Indication(s)	Classification of antibody	Testing needed before treatment	Testing needed during/after treatment	Laboratory test interference (References)	Initial US Approval
Muromonab-Cd3	Okt3	T-CD3	Transplant rejection	Murine	Renal function, LFTs, routine blood test	Renal function, LFTs, routine blood test	/	1986
Abciximab	Reopro	Glycoprotein IIb/IIIa receptor	Cardiac ischemic complications	Chimeric	PT, ACT, APTT, platelet count	ACT, APTT, platelet count	Pseudothrombocytopenia[4,5]	1994
Rituximab	Rituxan	CD20	NHL, CLL, RA, GPA, MPA	Chimeric	HBV	Routine blood test, renal function tests	/	1997
Basiliximab	Simulect	CD25	Renal transplantation	Chimeric	/	/	/	1998
Infliximab	Remicade	TNF-α	(pediatric)CD, (pediatric) UC, RA, AS, Ps, PsA	Chimeric	TB, HBV	HBV, malignancies, LFTs	/	1998
Palivizumab	Synagis	RSV F-protein	RSV infection	Humanized	/	/	RSV diagnostic test([6])	1998
Trastuzumab	Herceptin	HER2	Breast cancer, metastatic gastric cancer	Humanized	LVEF, HER2, pregnancy status	LVEF, neutrophile granulocyte	/	1998
Alemtuzumab	Lemtrada	CD52	MS	Humanized	Thyroid function	Thyroid function, CBC	/	2001
	Campath	CD52	CLL,CTCL	Humanized	/	CBC, CMV	/	2001
Adalimumab	Humira	TNF-α	RA, JIA, PsA, pediatric (CD), AS, UC, Ps	Humanized	Active TB, latent infection	Active TB	/	2002
Ibritumomab tiuxetan	Zevalin	CD20	NHL	Murine	/	CBC	Platelet function or coagulation[7,8]	2002
Omalizumab	Xolair	IgE	Asthma, idiopathic urticaria	Humanized	Blood test for IgE (for asthma patients)	Geohelminth infection,	IgE levels[9,10]	2003
Cetuximab	Erbitux	EGFR	Head and neck cancer, colorectal cancer	Chimeric	/	Electrolyte, dermatologic toxicities	/	2004
Natalizumab	Tysabri	Integrin α4	MS, CD	Humanized	JCV	Cerebrospinal fluid analysis for JC viral DNA, LFTs	/	2004
Bevacizumab	Avastin	VEGF	mCRC	Humanized	/	Blood presure, urine protein, proteinuria/24 hours	/	2004
Abatacept	Orentia	CTLA4	RA, JIA	Humanized	/	/	Blood glucose[11,12]	2005
Panitumumab	Vectibix	EGFR	mCRC	Fully human	/	Dermatologic/soft tissue toxicities, electrolytes, keratitis	/	2006
Ranibizumab	Lucentis	VEGF	Macular degeneration	Humanized	Intraocular pressure	Eye infection, intraocular pressure	/	2006
Eculizumab	Soliris	C5	PNH, aHUS	Humanized	/	Routine blood, blood clots, creatinine, LDH	/	2007

(Continues)

TABLE 1 (Continued)

Generic name	Trade name	Target(s)	Indication(s)	Classification of antibody	Testing needed before treatment	Testing needed during/ after treatment	Laboratory test interference (References)	Initial US Approval
Certolizumab pegol	Cimzia	TNF-α	CD, RA, PsA, AS	Humanized	HBV, TB	/	aPTT[13,14]	2008
Canakinumab	Ilaris	IL-1β	CAPS, FCAS, MWS, SJIA	Fully human	TB	/	/	2009
Golimumab	Simponi	TNF-α	RA	Fully human	TB, HBV	TB	/	2009
Ofatumumab	Arzerra	CD20	CLL	Fully human antibody	HBV	HBV, renal function, electrolye, hepatitis, CBC	/	2009
Ustekinumab	Stelara	IL-12, IL-23	Ps, PsA	Fully human	Mycobacteria, salmonella and BCG vaccinations, TB	TB	/	2009
Denosumab	Prolia	RANKL	Osteoporosis in postmeno-pausal women	Fully human	Calcium levels	Calcium levels	/	2010
	Xgeva	RANKL	Skeleton-related events	Fully human	Calcium levels	Calcium levels	/	2010
Tocilizumab	Actemra	IL - 6	RA, PJIA, SJIA	Humanized	TB	LFTs, neutrophils, platelets, blood lipid	/	2010
Belimumab	Benlysta	Bly-S	SLE	Fully human	/	/	/	2011
Ipilimumab	Yervoy	CTLA-4	Unresectable or metastatic melanoma	Fully human	LFTs, clinical chemistries, ACTH level, thyroid function	LFTs, clinical chemistries, ACTH level, thyroid function, enterocolitis, dermatitis, neuropathy, hypophysitis, adrenal insufficientcy, hyper- or hypothyroidism	/	2011
Belatacept	Nulojix	CTLA4	Rejection following renal transplantation	Humanized	/	TB	/	2011
Brentuximab Vedotin	Adcetris	CD30	Hodgkin's lymphoma, ALCL	Humanized	CBC	CBC, fever, liver enzymes, bilirubin	/	2012
Pertuzumab	Perjeta	HER2	(metastatic) HER2-positive breast cancer	Humanized	HER2, pregnancy status	LVEF	/	2012
Raxibacumab	Abthrax	Bacillus anthracis	Inhalation anthrax	Fully human	/	/	/	2012
Obinutuzumab	Gazyva	CD20	CLL	Humanized	HBV	Platelet counts, HBV, renal function tests, electrolyte	/	2013
Ado-Trastuzumab	Kadcyla	Her2	Breast cancer	Humanized	Platelet counts, serum transaminases, bilirubin, LVEF	Serum transaminases, bilirubin, platelet counts, neurotoxicity, LVEF	/	2013
Blinatumomab	Blincyto	CD19, T-CD3	Acute lymphoblastic leukemia	Murine	ALT, AST, GGT, total blood bilirubin	Neurological toxicities, white blood cell count, neutrophil count	/	2014

(Continues)

TABLE 1 (Continued)

Generic name	Trade name	Target(s)	Indication(s)	Classification of antibody	Testing needed before treatment	Testing needed during/after treatment	Laboratory test interference (References)	Initial US Approval
Nivolumab	Opdivo	PD-1	Metastatic melanoma	Fully human	LFTs, thyroid function, serum creatinine, pregnancy status	LFTs, thyroid function, renal function, serum creatinine, neurologic function, pneumonitis, colitis, endocrinopathies, nephritis, rash, encephalitis	/	2014
Pembrolizumab	Keytruda	PD-1	Melanoma	Humanized	/	Hepatic function, renal function, thyroid function, pneumonitis, colitis, hypophysitis	/	2014
Ramucirumab	Cyramza	VEGFR-2	Stomach cancer, esophageal cancer, lung cancer	Fully human	/	Blood pressure, urine protein, proteinuria/24 hours, thyroid function	/	2014
Siltuximab	Sylvant	IL - 6	MCD	Chimeric	HIV, HHV-8	/	/	2014
Vedolizumab	Entyvio	Integrin α4β7	UC, CD	Humanized	TB	JCV	/	2014
Alirocumab	Praluent	PCSK9	HeFH, ASCVD	Fully human	/	/	/	2015
Daratumumab	Darzalex	CD38	Multiple myeloma	Fully human	Serological testing	/	Cross-matching and red blood cell antibody screening, serological testing, indirect Coombs test, SPE, IFE[15-18]	2015
Dinutuximab	Unituxin	GD2	Neuroblastoma	Chimeric	/	Blood pressure, peripheral blood counts, electrolyte	/	2015
Elotuzumab	Empliciti	SLAMF7	Multiple myeloma	Humanized	/	LFTs	SPE, IFE[19]	2015
Evolocumab	Repatha	PCSK9	HeFH, CVD	Humanized	/	/	/	2015
Idarucizumab	Praxbind	Dabigatran	Anticoagulant effects of dabigatran	Humanized	/	/	/	2015
Mepolizumab	Nucala	IL-5	Severe asthma	Humanized	/	/	/	2015
Necitumumab	Portrazza	EGFR	Squamous non-small cell lung cancer	Fully human	Blood magnesium	Serum electrolytes, dermatologic toxicities, VTE, ATE	/	2015
Secukinumab	Cosentyx	IL-17A	Ps	Fully human	TB	TB	/	2015
Atezolizumab	Tecentriq	PD-L1	Urothelial cancer	Humanized	Hepatitis, AST, ALT, bilirubin	Hepatitis, AST, ALT, bilirubin, diarrhea/colitis, endocrinopathies, meningitis/encephalitis	/	2016
Ixekizumab	Taltz	IL-17A	Plaque psoriasis	Humanized	TB	/	/	2016

(EGFR) (Table 1). The skin toxicity is thought to be due to the expression of the target antigen, EGFR, on human keratinocytes. Usually, tests for electrolyte and dermatologic toxicities are need for patients receiving cetuximab treatment (Table 1). Non-specific toxicity may also occur during treatment with mAbs; for example, hypersensitivity reactions are commonly observed that are thought to be related to the immunogenicity of mAbs.[25] The immunogenicity is ability of a particular substance to induce an immune response in human body. In 1986, muromonab-CD3 (trade name Orthoclone OKT3) was approved by the US Food and Drug Administration (FDA) as the first therapeutic mAb (Table 1), which was used to reduce acute rejection in organ transplant patients.[26] However, these early products were murine antibodies, which led to allergic reactions and reduced the efficacy of the drugs. Following progress made in recombinant DNA technology, the technology developed from the use of murine mAb to chimeric mAb to humanized mAb and ultimately to fully human mAb.[1] Currently some mAbs still contain non-human sequences, which would be recognized as 'foreign' substance by human body. The mAbs with a high proportion of non-human sequences are likely to be recognized as 'foreign' and therefore induce an unwanted immune response, which often harms human body. It is important to note that the main factor affecting the immunogenicity of the mAbs is the proportion of human vs non-human sequences. Therefore, some clinical laboratory tests are needed to monitor the safety of patients receiving treatment of such mAbs. For example, renal function, LFTs and routine blood test are needed for patients receiving Muromonab-CD-3 treatment (Table 1).

Early diagnosis and close clinical monitoring are essential for the successful management of adverse events during treatment with mAbs. It is crucial for clinicians to test the corresponding indicators of these reactions in real time. In the event of a severe side effect, dose adaptation, a change in treatment, or complete cessation of treatment should be implemented if necessary. Table 1 presents the reported side effects of the various therapeutic mAbs. Therefore, clinical laboratory tests are needed during/after treatment of most of current FDA-approved mAb drugs (Table 1).

4.3 | Clinical laboratory tests influenced by mAb treatment

Since the 1970s when mAb technology was developed, mAbs have become common and essential research and clinical diagnostic tools for many applications, including enzyme-linked immunosorbent assays (ELISAs), Western blotting, immunohistochemistry, immunoprecipitation, and cytometric analysis. The use of mAbs is important for the identification of proteins, carbohydrates, and nucleic acids. Compared to polyclonal antibodies, the mAbs have been proved to be more sensitive and specific. Because mAbs are widely used for both clinical diagnostics and disease treatment, there may be cross-reactions for some laboratory tests. For example, palivizumab, a therapeutic mAb against respiratory syncytial virus (RSV) F glycoprotein, has been observed to interfere with immunologically based RSV diagnostic assays in laboratory studies.[27] As required, the label for the drug points out that it is not possible to test for RSV infection using an immunoassay during treatment with palivizumab, and reverse transcriptase-polymerase chain reaction (RT-PCR) should be used instead. In other cases, the interference is unexpected. For example, abatacept, which targets CTLA4, interferes with blood glucose testing (Table 1). The drug label contains this information, but serves as a reminder that physicians and laboratory personnel should be aware of potential drug-laboratory test interference.

Among the FDA-approved mAb drugs, only a small group of them would interference clinical laboratory tests. Accurately, now there are eight FDA-approved mAb drugs interfere with 10 clinical laboratory tests (Table 1). Daratumumab is the most influencing mAb, which interferes with five clinical laboratory tests. Elotuzumab interfere with two clinical laboratory tests. The other six mAbs each interfere with only one clinical laboratory test (Table 1).

5 | PERSPECTIVES: WHEN, WHY, AND WHAT IS EXPECTED FOR LABORATORY TESTS?

Since the commercialization of the first therapeutic mAb product in 1986, this class of agents has been used in a variety of clinical treatments, including those for cancer, allograft rejection, autoimmune disorders, infectious diseases, and inflammatory disorders. As biotechnology and bioinformatics continue to advance, new targets for therapeutic mAb will be found and studied.[22,28,29] In fact, there is already a higher approval rate for mAbs than other biopharmaceutical products, and the global sales of monoclonal antibody products have grown faster than those of other products in recent years.[30] The last decade has witnessed a more extensive and widespread use of therapeutic mAb in clinical treatment. Based on the current approval rate of new products per year, there should be 70 therapeutic mAb products on the market by 2020, and combined worldwide sales will be nearly $125 billion.[30] Thus, there is a need to continue investigations into the testing that should be performed before, during, and after treatment with mAbs, and extensive surveillance to determine what laboratory tests may be affected by treatment with these agents.

The therapeutic mAbs exhibit high specificity for their targets. The efficacy of a mAb depends on the characteristics of the targeted antigen, including its function, the cell-surface density and tissue distribution, as well as the characteristics of the mAb, including its specificity, avidity, and isotype. These factors are also associated with the risk of adverse effects for these mAbs.

Therapeutic mAbs can induce unexpected interference with laboratory tests via several mechanisms, including direct cross-reactions with the test reagents, the suppression of physiological functions in the patient, activation of inflammatory processes after binding of the mAb to its target.[31] Detecting or knowing about the interference and using an alternative method to run the laboratory test are critical to ensure the accuracy of results and safety of patients.[20] It is critical to eliminate the influence of interference on clinical practice. The most practical strategy for managing the concerns about laboratory interference is to enhance the communication between the laboratory staff

and clinicians. When laboratory reports show non-conformity with the status or medication history of the patient, the possibility of interference should be considered and investigated. In addition, the incorporation of such information into automated laboratory software would help to alert staff members to potential interference.

6 | CONCLUSION

Drug labels are legal documents that contain all of the important information about a given drug, and provide legal guidance regarding the use of the medication. Hence, it is important for the manufacturer to provide all related information as precisely and in the greatest detail possible. As such, the US FDA has promulgated a series of standards to explicitly guide the production of drug labels.[32,33]

Although the DailyMed database provides a convenient source of drug labels, clinicians and laboratory personnel may not have the time to search for and keep abreast of the laboratory tests affected by mAbs. Therefore, we herein provided this report which offers comprehensive and convenient information regarding the clinical laboratory tests associated with various mAbs. The information includes both the testing that should be performed before, during, or after treatment, and the potential interference that may be encountered. We believe that our brief report and the included table can serve as a handy reference for clinical laboratory staff and clinicians to provide better diagnostic services and treatment.

In conclusion, we have herein provided a comprehensive summary of the interference reported for the current FDA-approved therapeutic mAbs, as well as a list of the tests that must be performed before, during or after treatment to ensure the best patient outcome.

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AUTHOR CONTRIBUTIONS

Z.Z., W.H., L.L., and H.D. collected the data, performed the initial analyses, and wrote the manuscript; H.L. designed and oversaw the study. All authors were involved in the interpretation of the data and development of the manuscript, and approved the final manuscript for submission.

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