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Review

Pharmacological interactions of monoclonal antibodies☆

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ABSTRACT

The pharmacological interactions of biological agents are not well known. Because biologic agents are not metabolized by cytochrome P450 (CYP) enzymes and do not interact with cell membrane transporters, it is generally perceived that they are free from interactions with small molecule drugs. However, the clearance of biological agents varies depending on the modulation of the immune response or by either increasing or reducing the expression of target cells of the biological agents, which can occur through the action of multiple synthetic chemical agents. Furthermore, some biological agents may modify the metabolism of chemical drugs through their effects on the expression of P450 system enzymes. In this review, we will provide an outline of the pharmacokinetics properties and pharmacologic interactions of biological drugs, focusing on monoclonal antibodies, and how these can interact with chemical synthesis molecules. We believe knowledge of them is important for clinicians and affects multiple clinical specialties.

Interacciones farmacológicas de los anticuerpos monoclonales

Palabras clave:
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RESUMEN

Las interacciones farmacológicas de los agentes biológicos no son bien conocidas. Debido a que los fármacos biológicos no son metabolizados por las enzimas del citocromo P450 (CYP450) ni interaccionan con los transportadores transmembrana, existe la percepción de que estos no presentan interacciones medicamentosas con los fármacos de síntesis química. Sin embargo, el aclaramiento de los agentes biológicos puede variar en función de la respuesta inmune o si se modifica la expresión de sus células diana, lo cual puede ocurrir por la acción de muchos agentes químicos. Además, algunos biológicos son capaces de modular la expresión de las enzimas del sistema CYP450. En esta revisión, se proporciona una descripción de las propiedades farmacocinéticas y posibles interacciones de los fármacos biológicos, centrándonos en los anticuerpos monoclonales, y como estos pueden interaccionar con las moléculas de síntesis química. Creemos que su conocimiento es importante para los clínicos y afecta a varias especialidades médicas.

Introduction

Since the first biologic drugs were released in the mid-1980s, more than 40 different agents have been approved, including monoclonal antibodies (mAbs), growth factors, cytokines, fusion proteins and peptide hormones. These have revolutionized the current pharmacotherapy of many diseases: oncological, autoimmune, cardiovascular or inflammatory. Traditionally its use has been limited in part due to its high cost or the often-unpredictable clinical consequences that these could trigger, especially due to their immunogenic characteristics.

In recent years, largely due to the emergence of biosimilar drugs and the advance in the knowledge of their management, their use has grown exponentially. In fact, in 2014, mAbs occupied the sixth place in overall drug sales around the world[1] and this trend seems to be increasing as indicated by the numerous studies that are currently being conducted for the development of these drugs[2] (Table 1).

Therefore, clinicians face a new era in pharmacological therapy, a very different context in terms of chemical, pharmacokinetic and pharmacodynamic characteristics when compared with traditional

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Table 1
Monoclonal antibodies currently approved (EMA/FDA).

Molecule (trade name)	Year of approval	Action target	Type of antibody	Main indications
Abciximab (Reopro®)	1995	GPIIb/IIIa	Chimaeric	Angina, coronary disease
Rituximab (MabThera®, Rituxan®)	1998	CD20	Chimaeric	Lymphomas, SAD
Basiliximab (Simulect®)	1998	IL2R	Chimaeric	Acute organ rejection
Palivizumab (Synagis®)	1999	RSV	Humanized	RSV
Infliximab (Remicade®)	1999	TNF	Chimaeric	SAD
Trastuzumab (Herceptin®)	2000	HER2	Humanized	Breast, gastric Ca
Alemtuzumab (MabCampath, Campath-1H®)	2001	CD52	Humanized	Multiple sclerosis
Adalimubab (Humira®)	2013	TNF	Human	SAD
Tositumomab-I131 (Bexxar®)	2003	CD20	Murine	Lymphomas
Cetuximab (Erbitux®)	2004	EGFR	Chimaeric	Head, neck and colorectal Ca
Ibritumomab tiuxetan (Zevalin®)	2004	CD20	Murine	Lymphomas
Omalizumab (Xolair®)	2005	IgE	Humanized	Asthma, retinitis
Bevacizumab (Avastin®)	2005	VEGF	Humanized	rectum, colon, breast, NSCLC Ca...
Natalizumab (Tysabri®)	2006	α4-integrin	Humanized	Sclerosis
Ranibizumab (Lucentis®)	2007	VEGF	Humanized	Macular oedema
Panitumumab (Vectibix®)	2007	EGFR	Human	Colorectal cancer
Eculizumab (Soliris®)	2007	C5	Humanized	PNH, HUS, MG
Certolizumab pegol (Cimzia®)	2009	TNF	Humanized	SAD
Golimumab (Simponi®)	2009	TNF	Human	Idem
Canakinumab (Ilaris®)	2009	IL1b	Human	Idem
Ustekinumab (Stelara®)	2009	IL1/223	Human	CD
Tocilizumab (RoActemra, Actemra®)	2009	IL6R	Humanized	RA, Still
Ofatumumab (Arzerra®)	2010	CD20	Human	Leukaemia, lymphomas
Denosumab (Prolia®)	2010	RANK-L	Human	Osteoporosis
Belimumab (Benlysta®)	2011	BLyS	Human	SLE
Ipilimumab (Yervoy®)	2011	CTLA-4	Human	Melanoma
Brentuximab vedotin (Adcentris®)	2012	CD30	Chimaeric	Lymphomas
Pertuzumab (Perjeta®)	2012	HER2	Humanized	Breast Ca
Raxibacumab (Abthrax®)	2013	*B. anthracis*	Human	Anthrax
Infliximab biosimilar (Remsima®: Inflectra and Flixabi)	2013	TNF	Chimaeric	SAD
Ramucirumab (Cyramza®)	2014	VEGF	Human	Digestive, lung Ca
Vedolizumab (Entyvio®)	2014	Integrin α4β7	Humanized	CD, UC
Pembrolizumab (Keytruda®)	2014	PD-1	Humanized	Lymphoma, melanoma, Ca lung
Situximab (sylvant®)	2014	IL-6	Chimaeric	Castleman's disease
Mepolizumab (Nucala®)	2015	IL-5	Humanized	Eosinophilic asthma
Alirocumab (Praluent®)	2015	PCSK9	Human	Hyperchol
Evolocumab (Repatha®)	2015	PCSK9	Human	Hyperchol
Dinutuximab (Unituxin®)	2015	GD2	Chimaeric	Neuroblastoma
Idarucizumab (Praxbind®)	2015	Dabigatran	Humanized	Dabigatran effect reversal
Secukinumab (Cosentyx®)	2015	IL-17a	Human	SAD
Daratumumab (Darzalex®)	2015	CD38	Human	Multiple myeloma
Ixekizumab (Talz®)	2017	IL-17a	Humanized	Psoriasis
Elotuzumab (Empliciti®)	2017	SLAMF7	Humanized	Multiple myeloma
Obinutuzumab (Gazyvaro®)	2017	CD20	Humanized	Leukaemia, lymphoma

RA: rheumatoid arthritis; B: bacillus; BLyS: B lymphocyte stimulator; C5: C5 fraction of the complement; Ca: cancer; DC: differentiation cluster; NSCLC: non-small cell lung cancer; CTLA-4: cytotoxic antigen of T lymphocytes; UC: ulcerative colitis; SAD: systemic autoimmune diseases; CD: Cröhn's disease; EGFR: epidermal growth factor receptor; EpCAM: epithelial cell adhesion molecule; HER: human epidermal growth factor receptor; Hyperchol: hypercholesterolemia; PNH: paroxysmal nocturnal haemoglobinuria; IL: interleukin; SLE: systemic lupus erythematosus; MG: myasthenia *gravis*; PCSK9: proprotein convertase subtilisin/kexin type 9; PD: programmed death; RANK-L: NF-kB activating receptor ligand; HUS: haemolytic uraemic syndrome; SLAM: signalling lymphocyte-activation molecule; Still: Still's disease; TNF: tumour necrosis factor; VEGF: vascular endothelial growth factor; RSV: respiratory syncytial virus.

pharmacological therapies mainly composed of small molecules (Table 2). This is especially relevant in polymedicated patients (polypharmacy), who can experience pharmacological interactions with both biologic and chemical synthesis drugs.

Because these drugs are not metabolized by the same route as traditional drugs (Table 3), the general perception is that this type of interactions would not have clinically significant consequences. However, the clinician has more and more biologic agents at his disposal, and its use in combination with chemically synthesized drugs, for example methotrexate (MTX), or tumour necrosis factor alpha (TNF-α) antagonists in the treatment of rheumatoid arthritis (RA)[3,4] or other biologic agents, such as nivolumab or ipilimumab in the treatment of melanoma[5] has become common practice. Therefore, it is necessary to know their nature and production mechanisms in a way that allows their successfully management in clinical practice.

Pharmacokinetics of monoclonal antibodies

Absorption

Due to their low oral bioavailability (they are rapidly degraded by proteolytic enzymes or denatured by the acidic pH of the stomach), all currently approved mAbs are administered parenterally, either in intravenous (IV) infusion, subcutaneously (SC) or intramuscular (IM).

After its IM or SC administration, mAbs absorption occurs through the lymphatic system. The high porosity of this system allows a convective transport of these by the different interstitial fluids. However, the process of exchange between the lymphatic fluid and the vascular system is a slow process, which explains why the absorption of mAbs from the injection site can take hours or even days. In human studies it has been observed that the