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Monoclonal Antibodies and Small-Molecule Drugs: WHAT GENERAL NEUROLOGISTS NEED TO KNOW

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Introduction

Numerous drug modalities have been approved to treat neurologic diseases, including small-molecule drugs (SMDs) and biologics such as monoclonal antibodies (mAbs).[1-3] While both are considered targeted therapies,[2-7] each has unique characteristics that may affect their use in clinical practice.[5,8,9] This article describes the general characteristics of SMDs and mAbs and discusses some of their safety implications relevant to their use by general neurologists in clinical practice.

Characteristics of SMDs and mAbs

The general characteristics and pharmacokinetics (PK) of SMDs and mAbs are summarized in **Table 1**.[5,8-11] SMDs are small (~0.5 kDa), relatively simple chemical entities[8,12] produced through chemical synthesis, which is mechanically controlled and results in identical copies each time.[8,10] Therapeutic mAbs are large (~150 kDa), complex proteins[8,10,12] purified from living cells; their manufacture involves a complex process requiring multiple quality control steps to facilitate consistency.[8,10,13,14]

Due to their molecular and biologic characteristics, SMDs and mAbs have unique properties with regard to drug target and specificity. SMDs, particularly those that are lipid soluble, can be directed at intracellular or extracellular targets.[2,8] Because their large size precludes crossing cellular membranes, mAbs are generally directed at extracellular targets[8-10] and can be designed to selectively disrupt receptor–ligand interactions.[6] mAbs are also highly selective for a single antigen,[8,15,16] a biologic characteristic that has been harnessed to generate therapeutics with high target specificity.[8]

The ways in which the body absorbs, metabolizes, and eliminates SMDs and mAbs may affect dosing, administration, and the types of tissues that can be reached.[5,9,10,12] SMDs and mAbs have unique PK characteristics;[9,10,17,18] simulated PK profiles for each treatment modality are illustrated in **Figure**.[9,17,18] SMDs typically require daily dosing,[4,8,9] and administration is usually oral.[8,10] Because of the long half-life of mAbs,[19] dosing can be monthly[5,6,8,9,20] or even quarterly.[5,6] As large, hydrophilic glycoproteins that tend to denature in the stomach and degrade within the gastrointestinal tract,[9] mAbs are administered parenterally (typically via intravenous [IV] or subcutaneous [SC] injection).[8-10] Each dosing regimen and administration route has advantages and disadvantages, especially regarding patient preference and ease of use. Some patients report improved adherence with compounds dosed less frequently,[6,9] but patients with needle phobia or other injection-related concerns may prefer oral administration.[21] Absorption is relatively slower with SC administration (time to peak plasma concentration 1–8 days) than IV, but this route permits self-administration at home.[9,22]

SMDs generally have wide distribution into tissues, organs and plasma.[10,23] They are metabolized by CYP450 enzymes via oxidation, leading to renal elimination in the urine, and by conjugation reactions (eg, glucuronidation), leading to hepatic/biliary elimination in the stool.[10,24,25] mAbs have a small range of distribution.[10,23] Particularly relevant to neurology, therapeutic mAbs do not readily cross the blood–brain barrier and therefore have minimal distribution in the central nervous system (CNS).[8,9] Therapeutic mAbs are also too large for clearance by renal or hepatic mechanisms, and instead are metabolized by two primary pathways: nonspecific elimination via the reticuloendothelial system, and target-mediated (antigen-mediated) clearance via internalization of the mAb–target complex into the target cell, followed by intracellular degradation.[5,8-10,16,26]

Safety Considerations

The properties of SMDs and mAbs discussed above have important implications for the safety of these treatment modalities. SMDs have the potential to cross the blood–brain barrier, which may result in a risk of CNS-related adverse effects (AEs) such as dizziness, somnolence, and cognitive dysfunction.[27-29] Since mAbs have minimal distribution in the CNS, they are not typically associated with CNS-related AEs.[9]

The likelihood of drug–drug interactions (DDIs) depends on the characteristics of the therapeutics administered.[24,25] Because they share a common metabolic and elimination pathway via the kidney and liver, coadministration of multiple SMDs may result in DDIs;[24,25] therefore, monitoring the risk of DDIs is important.[10] Coadministration of SMDs and mAbs is not expected to result in DDIs because mAbs are not metabolized or eliminated by CYP450 enzymes or cell membrane transporters.[10,24]

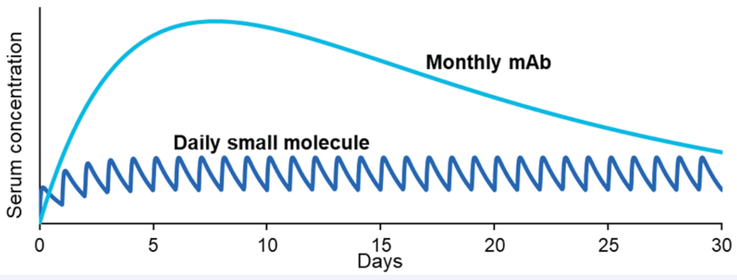
mAbs are associated with two main types of toxicity: target-related effects and target-independent toxicities (including immunogenicity).[8,10] Target-related AEs may involve intended cellular effects at the intended target tissue (eg, immunosuppressive mAbs to treat inflammation leading to infection), or unintended cellular effects due to mAb interactions with the target antigen at an unintended tissue (eg, antitumor mAbs targeting epidermal growth factor receptor leading to skin AEs).[8] Immunogenicity, which refers to the development of an anti-drug antibody (ADA) host response to the therapeutic mAb, occurs independent of the mAb target and is a potential risk with all therapeutic mAbs.[8,23] ADAs can reduce target binding, alter PK parameters, decrease therapeutic efficacy, and induce infusion reactions (including hypersensitivity).[5,8] The immune-complex formed

TABLE 1. Characteristics of Monoclonal Antibodies and Small-Molecule Drugs[5,8-11]

	Small-Molecule Drugs	Monoclonal Antibodies
General characteristics[5,8-11]		
Size	Low MW (eg, ~0.5 kDa)	High MW (eg, ~150 kDa)
Structure	Chemical	Protein (immunoglobulin)
Production	Chemically synthesized; mechanically controlled and resulting in identical copies each time	Culture derived; requires multiple quality control steps to ensure consistency
Stability	Independent of external conditions	Sensitive to external conditions
Targets	Intracellular/extracellular	Extracellular
Target specificity	Lower	High
Crosses BBB	Potentially	Minimal
DDIs	More likely	Less likely
Immunogenicity	Unlikely	Possible
Administration	Usually oral	Parenteral
Dosing frequency	Daily or ≥1 time per day	Every other week to yearly
PK properties[5,8-10]		
Absorption	Capillaries	Mainly lymphatic system
Distribution	Wide (organs and tissues)	Limited (difficult to reach organs and tissues)
Metabolism	Mainly CYP450 and conjugation reactions; nonactive and active metabolites	Metabolized/catabolized into peptides or amino acids
Excretion	Mainly liver, kidney	RES; mostly recycled as peptide fragments by the body
Half-life	Short; often hours	Long; often days to weeks

Abbreviations: BBB, blood–brain barrier; CYP450, cytochrome P450; DDIs, drug–drug interactions; MW, molecular weight; PK, pharmacokinetic; RES, reticuloendothelial system.

FIGURE. Simulated pharmacokinetic profiles for a small-molecule drug (daily oral dosing) and a therapeutic monoclonal antibody (mAb; monthly subcutaneous dosing).[9,17,18]



between mAb and ADA can also induce AEs.[30] Efficacy reductions or PK alterations due to neutralizing or non-neutralizing antibodies may necessitate dose modifications.[31] Patient-specific factors affecting immunogenicity include immunologic status (eg, immunocompetence), prior sensitization and history of allergy, immune tolerance to endogenous proteins, genetic predisposition, and dosing regimen (route of administration, dose, and frequency).[31] Historically, the likelihood of immunogenicity has decreased over time as mAbs have evolved from fully murine to fully human.[8]

Special Patient Populations

Certain considerations may be necessary when prescribing targeted therapies to special patient populations (**Table 2**).[7-10,12,24-26,31-41] Because of SMDs' route of elimination, their PK may be altered

TABLE 2. Considerations in Special Patient Populations[7-10,12,24-26,31-41]

Patient Population	SMD		mAb	
	Property	Dosing Considerations	Property	Dosing Considerations
Genetic polymorphisms in CYP450 enzymes[10,24,25,32,33,41]	Very slow or extremely rapid metabolism	• Lower or higher dosages • Extra monitoring • Potential DDIs	mAbs that are cytokine modulators may affect CYP-mediated drug metabolism	Cytokine modulators may require monitoring and dose adjustment
Hepatic impairment[7,10,12]	Possible elevation of liver enzymes	• Dose reduction • Potential contraindication for severe hepatic impairment	Unlikely to affect exposure to mAbs	Unlikely that >20% of dose undergoes hepatic catabolism
Renal impairment[7,10,12]	Reduced clearance and longer half-life	• Dose reduction or alternate treatments	Renal elimination is considered insignificant for biologics >69 kDa	Dosing reduction for biologics <69 kDa
Geriatric (progressive renal and hepatic impairment)[9,12,24,25,39]	• Possible elevation of liver enzymes • Reduced clearance and longer half-life	• Dose modifications • Potential DDIs	Possible effect on PK parameters with some mAbs	Scarce clinical pharmacology data available
Pregnancy, breastfeeding[8,34-38]	Small size allows transfer across placenta and into breast milk	Possible fetal exposure	Can cross placenta (typically after first trimester) and may be present in breast milk	Possible fetal exposure
Pediatric[12,40]			Potential differences in PK parameters between different age groups	• Use caution/dose conservatively • Body-weight/BMI dosing
Obese[26,39]	Altered elimination due to altered renal and hepatic blood flow; differences in metabolism	Dose adjustment and monitoring	No effect on clearance	Dosing unlikely to be affected
Immune system disorders[10,12,31]			• Immunogenicity • Immunosuppressed: less likely to mount immune response to therapeutic mAbs • Immunoactivated: may have amplified response to mAbs	• Concomitant use of immunosuppressive agents may decrease immune response to mAbs • SC dosing may result in increased immunogenicity vs IV and IM routes due to increased risk of exposure to NK cells and phagocytes present in mucosal epithelia and under the skin • Large continuous dose may be less immunogenic than smaller intermittent dosing

Abbreviations: BMI, body mass index; CYP450, cytochrome P450; DDIs, drug–drug interactions; IM, intramuscular; IV, intravenous; mAb, monoclonal antibody; NK, natural killer; PK, pharmacokinetic; SC, subcutaneous; SMD, small-molecule drug.

in patients with renal or hepatic impairment,[7,10,12,40] including that observed in geriatric patients.[39] Patients with immune system disorders may exhibit altered immunogenicity in response to therapeutic mAbs.[10,12,31] With regard to pregnant or breastfeeding women, the small size of SMDs allows them to cross the placenta and enter breast milk.[34,35] mAbs may be present in breast milk,[8,35] but typically do not cross the placenta until the second trimester.[35-38] Additional patient populations warranting special attention include pediatric patients[12,40] and patients with obesity, as detailed in **Table 2**.[26]

Summary

In sum, SMDs and mAbs have unique characteristics and PK properties, which relate to their safety profiles and suitability in special patient populations, and have important implications for their use in clinical practice.

REFERENCES

1. CenterWatch. www.centerwatch.com/directories/1067-fda-approved-drugs/topic/101-neurology. Accessed March 10, 2020.
2. Banks W, Greig N. *Future Med Chem*. 2019;11:489-493.
3. Voge N, Alvarez E. *Biomedicines*. 2019;7(1)pii E20.
4. Gerber DE. *Am Fam Physician*. 2008;77(3):311-319.
5. Levin M, Silberstein SD, Gilbert R, et al. *Headache*. 2018;58(10):1689-1696.
6. Scuteri D, Adornetto A, Rombolà L, et al. *Front Pharmacol*. 2019;10:363.
7. Mócsai A, Kovács l, Gergely P. *BMC Med*. 2014;12:43.
8. Foltz IN, Karow M, Wasserman SM. *Circulation*. 2013;127(22):2222-2230.
9. Silberstein S, Lenz R, Xu C. *Headache*. 2015;55(8):1171-1182.
10. Serra López-Matencio JM, Martínez Nieto C, Morell Baladrón A, Castañeda S. *J Immunol Sci*. 2018;2(2):4-7.
11. Kleinberg M, Wilkinson Mosdell K. *Am J Health-Syst Pharm*. 2004;61:695-710.
12. Zhao L, Ren T, Wang DD. *Acta Pharmacol Sin*. 2012;33(11):1339-1347.
13. Reason AJ, Weiskopf A, Rathore AS. *BioPharm Int*. 2014;27(7):34-43.
14. National Research Council (US) Committee on Methods of Producing Monoclonal Antibodies. *Monoclonal Antibody Production*. Washington, DC: National Academy Press; 1999.
15. Carter PJ. *Nat Rev Immunol*. 2006;6(5):343-357.
16. Tabrizi MA, Tseng C-ML, Roskos LK. *Drug Discov Today*. 2006;11(1-2):81-88.
17. Dhillon S, Gill K. In: Dhillon S, Kostrzewski A, eds. *Clinical Pharmacokinetics*. London: Pharmaceutical Press; 2006.
18. Davis JD, Deng R, Boswell CA, Zhang Y, Li J. In: Crommelin DJA, Sindelar RD, Meibohm B, eds. *Pharmaceutical Biotechnology: Fundamentals and Applications*. 4th ed. New York: Springer; 2013.
19. Robbie GJ, Criste R, Dall'acqua WF, et al. *Antimicrob Agents Chemother*. 2013;57(12):6147-6153.
20. Ovacik M, Lin K. *Clin Transl Sci*. 2018;11(6):540-552.
21. Spain CV, Wright JJ, Hahn RM, Wivel A, Martin AA. *Clin Ther*. 2016;38(7):1653-1664.e1.
22. Jin JF, Zhu LL, Chen M, et al. *Patient Prefer Adherence*. 2015;9:923-942.
23. Wan H. *ADMET & DMPK*. 2016;4(1):1-22.
24. Roberts AG, Gibbs ME. *Clin Pharmacol*. 2018;10:123-134.
25. Ogu CC, Maxa JL. *Proc (Bayl Univ Med Cent)*. 2000;13(4):421-423.
26. Hendrikx JJMA, Haanen JBAG, Voest EE, Schellens JHM, Huitema ADR, Beijnen JH. *Oncologist*. 2017;22(10):1212-1221.
27. D'Amico D, Tepper SJ. *Neuropsychiatr Dis Treat*. 2008;4(6):1155-1167.
28. Vécsei L, Majláth Z, Szok D, Csáti A, Tajti J. *Expert Opin Drug Saf*. 2015;14(5):667-668.
29. Pearlman EM, Doty EG, Dennehy EB, et al. *Headache*. 2019;59(suppl 1):22-23.
30. Krishna M, Nadler SG. *Front Immunol*. 2016;7:21.
31. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). *Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products*. 2014.
32. Belle DJ, Singh H. *Am Fam Physician*. 2008;77(11):1553-1560.
33. Zanger UM, Schwab M. *Pharmacol Ther*. 2013;138(1):103-141.
34. Rubinchik-Stern M, Eyal S. *Front Pharmacol*. 2012;3:126.
35. Kane SV, Acquah LA. *Am J Gastroenterol*. 2009;104(1):228-233.
36. Azim HA, Azim H, Peccatori FA. *Expert Rev Clin Immunol*. 2010;6(6):821-826.
37. Pitcher-Wilmott RW, Hindocha P, Wood CB. *Clin Exp Immunol*. 1980;41(2):303-308.
38. Gasparoni A, Avanzini A, Ravagni Probizer F, Chirico G, Rondini G, Severi F. *Arch Dis Child*. 1992;67(1 Spec No):41-43.
39. International Conference on Harmonisation. Guideline for Industry: Studies in Support of Special Populations: Geriatrics. 1994.
40. Matzke GR, Aronoff GR, Atkinson AJ, et al. *Kidney Int*. 2011;80(11):1122-1137
41. Christensen H, Hermann M. *Front Pharmacol*. 2012;3(9):1-10.