PHARMACOKINETIC CHARACTERISTICS OF MONOCLONAL ANTIBODIES AND IMPORTANCE IN THE PROCESS OF BIOSIMILAR REGISTRATION

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Monoclonal antibodies (mAbs) possess some unique pharmacokinetic properties as a consequence of their structure and function, making the development of mAbs substantially different from that of conventional drugs. After *s.c.* or *i.m.* application mAbs are absorbed through the lymphatic system by the convection process. Distribution to tissues is part of the elimination process, passage through cell membranes is limited by molecular mass and polarity, and a significant amount of mAbs is found in vascular and interstitial fluid. Despite a small volume of distribution, sufficient mAb concentrations are reached in target organs due to receptor-mediated uptake. For elimination of mAbs liver and kidneys are not considered essential, as mAbs are eliminatied through (a) nonspecific cell uptake followed by proteolytic degradation or (b) target mediated elimination, through interaction between the Fab region of the mAb and its target site. Long elimination half-life of mAbs is due to neonatal Fc receptor recycling, thus preventing mAbs degradation (1). Of all registered mAbs, so far only 6 have their biosimilars. An essential part of the mAb biosimilar development program, are comparative pharmacokinetic studies. These studies are designed to confirm similar pharmacokinetic profile of biosimilar with its reference mAt, in terms of both resorption and elimination. The design of these studies depends, among other factors, on the pharmacokinetic properties of the mAb, such as target mediated elimination, long elimination half-life, nonlinear pharmacokinetics, differences in pharmacokinetics between healthy subjects and patients, pharmacokinetic variability, changes in mAb distribution and elimination due to formation of anti-mAb antibodies (2).

References

1. Lazar-Molnar E, Delgado JC. Implications of monoclonal antibody therapeutics use for clinical laboratory testing. Clin Chem 2019;65(3):393–405.
2. EMA/CHMP/BMWP/403543/2010. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, 2012.

FARMAKOKINETIČKE SPECIFIČNOSTI MONOKLONSKIH ANTITELA I ZNAČAJ U PROCESU REGISTRACIJE BIOSIMILARA

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Monoklonska antitela (mAt) imaju jedinstvene farmakokinetičke karakteristike koje su posledica njihove strukture i funkcije, zbog čega je razvoj mAt značajno različit u odnosu na konvencionalne lekove. Posle *s.c.* ili *i.m.* primene mAt se resorbuju putem limfe procesom konvekcije. Distribucija u tkiva je deo procesa eliminacije, prolazak kroz ćelijske membrane ograničen je molekulskom masom i polarnošću, te se značajna količina mAt nalazi u vaskularnoj i intersticijalnoj tečnosti. Uprkos malom volumenu distribucije, u ciljnim organima se postižu dovoljne koncentracije mAt zbog receptorom posredovanog preuzimanja mAt. Za eliminaciju mAt jetra i bubrezi nisu od esencijalnog značaja, već se ona odvija (a) nespecifičnim preuzimanjem od strane ćelija posle čega sledi proteolitička degradacija ili (b) eliminacijom posredovanom ciljnim mestom, putem interakcije između Fab regiona mAt i njegovog ciljnog mesta. mAt imaju dugo poluvreme eliminacije zbog recikliranja posredstvom neonatalnog Fc receptora, čime se sprečeva degradacija mAt (1). Od velikog broja registrovanih mAt, za sada samo 6 ima svoje biosimilare. Esencijalni deo programa razvoja biosimilara mAt, a time i registracione dokumentacije su komparativne farmakokinetičke studije, dizajnirane tako da potvrde sličan farmakokinetički profil biosimilara sa referentnim mAt, ne samo u pogledu resorpcije, već i u pogledu eliminacije. Dizajn ovih studija, pored ostalog, zavisi i od farmakokinetičkih specifičnosti mAt, kao što su eliminacija posredovana ciljnim mestom, dugo poluvreme eliminacije, nelinearna farmakokinetika, razlike u farmakokinetici između zdravih i bolesnih ispitnika, varijabilnost farmakokinetike, promene u distribuciji i eliminaciji mAt zbog stvaranja anti-mAt antitela (2).

Literatura

1. Lazar-Molnar E, Delgado JC. Implications of monoclonal antibody therapeutics use for clinical laboratory testing. Clin Chem 2019;65(3):393–405.
2. EMA/CHMP/BMWP/403543/2010. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, 2012.