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# MANIFESTATION OF THE PARTICULARITIES OF THE USAGE FEATURES OF MONOCLONAL ANTIBODIES IN VARIOUS PHARMACOTHERAPEUTIC APPLICATIONS

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# მონოკლონური ანტისხეულების გამოყენების თავისებურებები სხვადასხვა ფარმაკოთერაპიული მიმართულებით

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

## რეზიუმე

მონოკლონური ანტისხეულები გამოიყენება სხვადასხვა სერიოზული დაავადებების სამკურნალოდ, როგორიცაა რევმატოიდული ართრიტი, მაანკილოზებელი სპონდილიტი, გაფანტული სკლეროზი, კიბო, ინფექციები და სხვა. მონოკლონურ ანტისხეულებს აქვთ იმუნომოდულატორული ეფექტი, მოქმედებენ სპეციფიკური ციტოკინების წინააღმდეგ, აფერხებენ სპეციფიკურ ფერმენტებს ან სასიგნალო მოლეკულებს. მონოკლონური ანტისხეულები ზოგადად კარგად გადაიტანება, მაგრამ თრგუნავენ იმუნურ სისტემას, რის გამოც შეუძლიათ განაახლონ ლატენტური ინფექციები, როგორიცაა ტუბერკულოზი ან B ჰეპატიტი. ონკოლოგიაში მონოკლონური ანტისხეულების უმეტესობა ინიშნება დოზირების სქემებში, სხეულის ზომის მიხედვით. მონოკლონური ანტისხეულების იმუნოთერაპია ახლა განიხილება კიბოს მკურნალობის ძირითად კომპონენტად ქირურგიასთან, სხივურ თერაპიასთან და ქიმიოთერაპიასთან ერთად. მონოკლონურ ანტისხეულებს აქვთ კლინიკურად შესაბამისი მოქმედების მრავალფეროვანი მექანიზმი. გარდა ამისა, ანტისხეულებს შეუძლიათ პირდაპირ მიმართონ სიმსივნურ უჯრედებს, ასევე ხელი შეუწყონ გრძელვადიანი სიმსივნის საწინააღმდეგო იმუნური რეაქციების ინდუქციას. მონოკლონური ანტისხეულების, როგორც თერაპიული პლატფორმის მრავალმხრივმა თვისებებმა განაპირობა კიბოს მკურნალობის ახალი სტრატეგიების შემუშავება, რაც დიდ გავლენას მოახდენს სიმსივნის მკურნალობაზე.

**Introduction.** Monoclonal antibodies (mAbs) are an important class of biological therapeutics and are used to treat diseases because of their anticancer and anti-inflammatory properties, as well as their ability to protect against respiratory infections. Its production involves post-translational glycosylation, a biosynthetic process for the conjugation of glycans to proteins that plays an essential role in the biological activity of mAbs, including effector functions and pharmacokinetics. More than 100 monoclonal antibodies are in development and their unique properties keep them in the therapeutic portfolio. Therefore, the therapeutic value and the elucidation of their pharmacological properties, which support the clinical development of these large molecules, are beyond doubt. However, their use as pharmacological tools in academic laboratories lags behind those of low molecular weight. Early therapeutic mAbs targeted soluble cytokines, but now that mAbs also target membrane-bound receptors and have a longer circulating half-life, their pharmacology has become more complex. Principles of pharmacology have enabled the development of potent and selective high affinity, low molecular weight therapies with reduced off-target effects and drug-drug interactions. This overview explains how the same basic principles can be applied to mAbs with some important differences. Monoclonal antibodies have several advantages such as: B. fewer side effects, fewer interactions with other drugs, higher specificity and possibly increased effectiveness through targeted therapy. Modifications to decrease immunogenicity and increase potency are described, with examples for optimizing their pharmacokinetic properties and providing oral bioavailability. Raising awareness of these advances could help expand their use in exploratory research and better understand and characterize their pharmacological properties. There are differences in drug distribution and elimination between patients. However, monoclonal antibodies are usually only distributed in the blood plasma and in the extracellular fluid, the number of which increases

disproportionately with increasing body weight. Elimination occurs via proteolytic catabolism, a nonspecific immunoglobulin G elimination pathway, and post-target intracellular degradation. The latter is the main route of elimination and depends on the target expression level and not on body size. In conclusion, the negligible effect of body size on the distribution and clearance of monoclonal antibodies and their generally wide therapeutic window do not justify body size-based dosing. The effects of body weight on the volume of distribution and clearance of monoclonal antibodies in oncology have been studied and it has been shown that a fixed dose is justified from a pharmacokinetic point of view for most of these medicinal products [1-4].

**Aim of the research** was to study and analyze manifestation of the particularities of the usage features of monoclonal antibodies in various therapeutic applications.

**Methodology:** The material of the article was the revised data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. Research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature. Use the following databases (for extensive literature searches to identify the key issues of features of prospects of use monoclonal antibodies in medicine): PubMed, Web of Science, Clinical key, Tomson Reuters, Google Scholar, Cochrane Library and Elsevier Foundations. National and international policies and guidelines were also reviewed and as well as grey literature.

**Results and Discussion.** Monoclonal antibodies are essential tools for many molecular immunology researches. Especially when combined with techniques such as epitope mapping and molecular modeling, monoclonal antibodies enable antigen profiling and visualization of macromolecular surfaces. In addition, monoclonal antibodies have become important components of various clinical diagnostic laboratory tests. Their wide application in the detection and identification of serum analytes, cell markers and pathogens are largely due to the excellent specificity of these unique reagents. In addition, the continuous culture of hybridoma cells that produce these antibodies allows for an unlimited supply of reagents. Compared to the rather limited range of polyclonal antibody reagents, the continuous supply essentially allows for a standardization of both the reagent and the test technique. It is clear that polyclonal and monoclonal antibodies have their advantages and disadvantages in terms of production, cost and general application. Ultimately, monoclonal antibodies are only made when needed, because while their production is time-consuming and frustrating, it is (most of the time, at least!) very rewarding. This is particularly evident when a monoclonal antibody can be used successfully in a routine pathology laboratory or aids in the clinical diagnosis and treatment of patients [5,6].

Monoclonal antibodies have recently attracted interest in the treatment of immune-mediated neuropathies, especially when there is evidence of underlying humoral pathogenic mechanisms.

Monoclonal antibodies targeting specific inflammatory cytokines are undoubtedly innovative drugs in many fields of medicine and have opened a new chapter in the treatment of severe and complex cases of immunological diseases. The same is true for severe asthma as we move from demanding and aggravating oral corticosteroid therapy to a more targeted and personalized immunological approach. In asthma, the use of monoclonal antibodies has allowed many patients to control their disease and significantly improve their quality of life. However, there remains a need to develop new effective treatments for more complex and rare cases, or in cases where existing treatments have proven ineffective [7-8].

Biological therapy targeting B cells appears to be an effective strategy for the treatment of various immune-mediated diseases. One of the best studied anti-B cell drugs is rituximab, an anti-CD20 monoclonal antibody that is an example of a B-cell depletion therapy and has served as a prototype for other anti-CD20 monoclonal antibodies and biosimilar development. Although there are many studies on the use of rituximab in dermatology, there is no comprehensive review of rituximab treatment for autoimmune skin diseases. This literature review provides a summary of the indications, treatment efficacy, and safety of rituximab in common autoimmune skin diseases: pemphigus vulgaris, cutaneous lupus erythematosus, dermatomyositis, systemic scleroderma, thyroid dermopathy, autoimmune pemphigoid diseases, diseases of the immune system, and cutaneous vasculitis. Existing data on rituximab support the approach of rituximab, biosimilars, and new treatments for immune-mediated skin diseases

that target B cells. Overall, CD20-targeting rituximab represents an effective alternative or complementary option to traditional immunosuppressants in the treatment of various autoimmune skin diseases. More research is needed to further understand and increase the potential benefits of B-cell targeting in autoimmune skin diseases [9,10].

Monoclonal antibodies have become the main type of antibody drugs because of their high specificity and high antigen affinity. However, in intensive studies of natural monoclonal antibodies, many disadvantages have been found, such as: B. limited antigen binding time, unexpected clearance of antibodies and accumulation of antigens. Therefore, research is no longer limited to screening for natural antibodies, but rather focuses on improving the performance of antibody-based drugs through engineering. Bottlenecks in conventional antibody development have been effectively eliminated in recent years with the discovery of a new recyclable antibody. The recirculating antibody binds to the antigen in the plasma and dissociates from the antigen in the endosome, thereby maximizing antibody utilization and reducing antigen-mediated clearance of the antibody and antibody-mediated accumulation of the antigen. In addition, antibody reuse can increase affinity for Fc receptors by further modifying Fc [11,12]. Although there are many immune checkpoints of T-cell activation, each checkpoint has distinct mechanisms. Consequently, ICB combinations that target multiple checkpoints will enhance T cell responses in a synergistic manner. The combination of mAbs targeting CTLA-4 and PD-1 performed significantly better in preclinical mouse models than either antibody alone. Similarly, in metastatic melanoma patients combined therapy of ipilimumab and nivolumab was found to be more effective than either treatment used as a monotherapy [13,14].

Monoclonal antibodies have become the mainstay of treatment for patients with relapsing forms of multiple sclerosis (RRMS) and offer certain benefits for patients with primary progressive MS. They are extremely accurate because they specifically target molecules present on cells involved in various immune mechanisms in the pathophysiology of multiple sclerosis. They differ not only in the target antigen they recognize, but also in the mechanism of action that reveals their therapeutic effect. Natalizumab, an integrin antagonist, binds to cell surface receptors, blocks interaction with their ligands, and thus prevents migration of leukocytes across the blood-brain barrier. On the other hand, alemtuzumab, the anti-CD52 monoclonal antibody, and the anti-CD20 monoclonal antibodies, rituximab, ocrelizumab, ofatumumab, and ubituximab, act by killing certain populations of pathogenic cells. However, possible side effects can be serious and require discontinuation of treatment. Most important is the risk of (opportunistic) infections and secondary autoimmune diseases or malignancies. Monoclonal antibodies also carry the risk of infusion/injection reactions, especially in the early stages of treatment. Careful patient selection and monitoring during treatment can minimize these potentially serious side effects. Monoclonal antibodies are characterized by a relatively long pharmacological half-life and pharmacodynamic effect, offering advantages such as the possibility of irregular dosing, but also disadvantages in terms of vaccination and family planning. This review provides an overview of currently available monoclonal antibodies for the treatment of RMS, including their mechanism of action, efficacy, and safety profile. In addition, there are practical recommendations for risk management, vaccination and family planning [15,16].

Antibody-based proteins have emerged as an important class of biological therapies, largely due to the stability, specificity, and adaptability of the antibody scaffold. Indeed, not only do antibodies have the inherent ability to bind to both antigens and endogenous immune receptors, but they have also proven to be extremely useful in protein engineering. Thus, various derivatives of the monoclonal antibody format, including bispecific antibodies, antibody-drug conjugates, and antibody fragments, have shown efficacy in the treatment of human diseases, particularly in the areas of immunology and oncology. Considerations for the development of antibody-based therapies, including immunological backgrounds, therapeutic mechanisms and technical strategies. First, antibody characterizations are presented with a focus on structural domains, functionally important receptors, isotypic and allotypic differences, and modifications such as glycosylation. Aspects of therapeutic antibody design are then discussed, including identification of antigen-specific variable regions, choice of expression system, use of multispecies formats, and design of antibody derivatives based on fragmentation, oligomerization, or conjugation with other functional

entities. Finally, strategies to improve antibody function through protein engineering are discussed, with a focus on the influence of fundamental biophysical properties on protein growth ability.

In the last twenty years, a new trend has prevailed in the daily practice of oncology: the gradual development towards individual and personalized care. The treatment of breast cancer is one of the best examples of the extraordinary effectiveness of an individual approach. Features of modern molecular pathology are able to predict the biological behavior of tumors and provide a new basis for our therapeutic choice, both for neoadjuvant and adjuvant therapy as well as for metastatic diseases. An overview of monoclonal antibodies currently used in the treatment of breast cancer was provided, as well as an overview of new research and future directions in this area.

**Conclusion.** In addition to surgery, radiation therapy, and chemotherapy, monoclonal antibody immunotherapy is now considered an integral part of cancer therapy. Monoclonal antibodies have several clinically relevant mechanisms of action. In addition, antibodies can be targeted directly to tumor cells and promote the induction of a long-term antitumor immune response. The diverse properties of antibodies as a therapeutic platform have led to the development of new cancer treatment strategies that will have important implications for cancer treatment. In addition, he discusses how monoclonal antibody strategies enhance the immune response against tumors by targeting immune cells rather than tumor antigens, and some current combination therapies.

***Conflict of interest:*** *All authors carefully read the given manuscript and approve the final version of this paper without any potential conflict of interest.*

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### SUMMARY

Monoclonal antibodies have been used for the treatment of various severe diseases, such as rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, cancer infections among others. They have immunomodulatory effects, are prepared against specific cytokines, inhibit specific enzymes or signaling molecules. Monoclonal antibodies are generally well tolerated, but those that suppress the immune system may reactivate latent infections, such as tuberculosis or hepatitis B. Most monoclonal antibodies in oncology are administered in body-size-based dosing schedules. Monoclonal antibody-based immunotherapy is now considered to be a main component of cancer therapy, alongside surgery, radiation, and chemotherapy. Monoclonal antibodies possess a diverse set of clinically relevant mechanisms of action. In addition, antibodies can directly target tumor cells while simultaneously promoting the induction of long-lasting anti-tumor immune responses. The multifaceted properties of antibodies as a therapeutic platform have led to the development of new cancer treatment strategies that will have major impacts on cancer care.

**Keywords:** Usage, features, monoclonal antibodies, clinical, therapeutic, applications