Open Access Research Journal of
Biology and Pharmacy
Journals home page: https://oarjbp.com/
ISSN: 2782-9979 (Online)

(REVIEW ARTICLE)

Detailed review on Bevacizumab and its target therapies

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Open Access Research Journal of Biology and Pharmacy, 2023, 09(01), 027–031

Publication history: Received on 28 August 2023; revised on 04 October 2023; accepted on 06 October 2023

Article DOI: https://doi.org/10.53022/oarjbp.2023.9.1.0042

Abstract

The review in this article focuses on bevacizumab, an agent widely used in a variety of treatment strategies. It provides an overview of the pharmacokinetics and pharmacodynamics of bevacizumab, with a focus on intravenous administration and available specific dose strengths. This article discusses treatment strategies with bevacizumab and emphasizes the importance of understanding its pharmacokinetic properties to optimize its efficacy. In addition, this review covers a wide range of side effects associated with bevacizumab, including cardiovascular, gastrointestinal, hematological, immune, musculoskeletal, nervous, renal, respiratory, and other side effects. The importance of close monitoring and prompt management of adverse events is emphasized to ensure patient safety and optimize patient outcomes. Overall, this literature review provides valuable insight into the use of bevacizumab and helps health professionals make informed decisions regarding dosing, monitoring, and management of side effects.

Keywords: Bevacizumab; Pharmacokinetics; Pharmacodynamics; Therapeutic strategy; Adverse reaction.

1. Introduction

A recombinant monoclonal antibody known bevacizumab binds to and renders inactive the biologic action of VEGF-A, preventing angiogenesis and, consequently, the development and proliferation of tumours. It is a humanised monoclonal IgG antibody with a molecular weight of 149 kDa that blocks all active VEGF isoforms by combining human framework sections with complementarity-determining domains from a murine antibody. Recombinant biotechnology is used to create bevacizumab from a Chinese hamster ovary mammalian cell line expression method. It retains the parental antibody's high levels of specificity and affinity for VEGF-A while having less immunogenicity and a longer biologic half-life that can last upto 21 days. [1]

The first medication licenced by the US Food and Drug Administration to prevent angiogenesis was bevacizumab. Bevacizumab underwent clinical trials for the treatment of early tumours before being licenced in 2009 for the treatment of recurrent glioblastoma. It has previously been used to treat a variety of metastasis. Human VEGF proteins were discovered in 1989 by a group of researchers, and they are thought to be among the most effective regulators of angiogenesis. A hypoxia inducible factor is hypothesised to be released in response to the oxygen and nutritional requirements of rapidly multiplying tumour cells, which then triggers the synthesis of VEGF. These proteins influence vascular permeability, angiogenesis, and vasculogenesis, as well as the development and migration of endothelial cells and the prevention of apoptosis. Arresting persistent angiogenesis is essential since it is a characteristic of many malignancies.[2]

2. Pharmacokinetics of bevacizumab

The pharmacokinetics of bevacizumab refer to the way the drug is absorbed, distributed, metabolized, and excreted by the body.

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2.1. Absorption of Bevacizumab

Large, difficult to cross cell membranes, and unable to tolerate digestive tract proteolysis are all characteristics of monoclonal antibodies (mAbs). Due to these properties, mAbs are not well absorbed when delivered orally and are instead given intravenously, intramuscularly, or subcutaneously. The pharmacokinetic characteristics of Avastin (bevacizumab) in a single dose (1 mg/kg) pharmacokinetic trial evaluating the bioequivalence of bevacizumab and TAB008 (a biosimilar product) were as follows 20: Cmax,the geometric mean, is 17.38 ug/mL. AUC inf geometric mean = 5,358 ugxh/mL Tmax in geometric terms is 2.50 hours.[3]

2.2. Digestion of Bevacizumab

Bevacizumab's volume of distribution has been estimated by a two-compartment model with first-order elimination to be 2.39 L for a typical female and 3.29 L for an average male, which is around the expected normal plasma volume.[4] Bevacizumab was shown to produce persistent serum levels of 10-30 g/ml in Cynomolgus monkey studies when given on a weekly basis at a dose of 2-3 mg/kg. This dose appeared to be sufficient to inhibit VEGF activity. Bevacizumab's extravascular distribution was modest and restricted to the tumor vasculature.[5]

2.3. Metabolism of Bevacizumab

Several processes exist for the clearance of monoclonal antibodies (mAbs). Target-independent pinocytosis and proteolysis, in which the liver and reticuloendothelial system (RES) break down mAbs into smaller amino acids and peptides, aretwo processes that contribute to non-specific clearance. When mAbs precisely bind with their target antigens, this is known as target-mediated clearance, and it results in clearance by lysosomal destruction. Anti-drug antibodies (ADA), which can combine with mAbs to create complexes, may also affect how quickly mAbs are cleared. The total removal of mAbs from the body is aided by these clearance routes.[6]

2.4. Excretion of Bevacizumab

Monoclonal antibodies cannot be excreted by the kidneys in a normal physiological state due to their size. Bevacizumab has an estimated half-life of 20 days;however, it can last anywhere between 11 and 50 days. Bevacizumab has an average daily clearance (CL) of 0.207 L.When a patient weigh >114 kg or 49 kg, the CL of bevacizumab might rise or fall by 30%.Bevacizumab typically clears from men's bodies 26% quicker than itdoes from women.The CL may change due to several other parameters, such as serum albumin,aspartate aminotransferase (AST), alkaline phosphatase (ALP), and tumor load.[7]

3. Pharmacodynamics of bevacizumab

Vascular endothelial-derived growth factor (VEGF) is a protein that binds to bevacizumab,preventing it from interacting with its receptors. Inhibiting downstream signaling, bevacizumab prevents the interaction of VEGF and its receptors. Bevacizumab's effects include: Restoring a more usual blood vessel network at the tumor site: Bevacizumab aids in the restoration of a more typical blood vessel network, potentially enhancing the flow ofnutrients and oxygen to the tumor. Increasing the delivery of chemotherapeutic drugs: Bevacizumab may increase the efficacy of chemotherapy in the targeted location by enhancing blood flow and vascular function. Bevacizumab's ability to block VEGF can result in both desired and unexpected outcomes. Inhibiting VEGF may slow the spread of metastatic illness, which is one of its intended benefits. Unintended consequences: Blocking VEGF has the potential to interfere with other physiological systems that depend on VEGF.[8]

3.1. Mechanism of action of bevacizumab

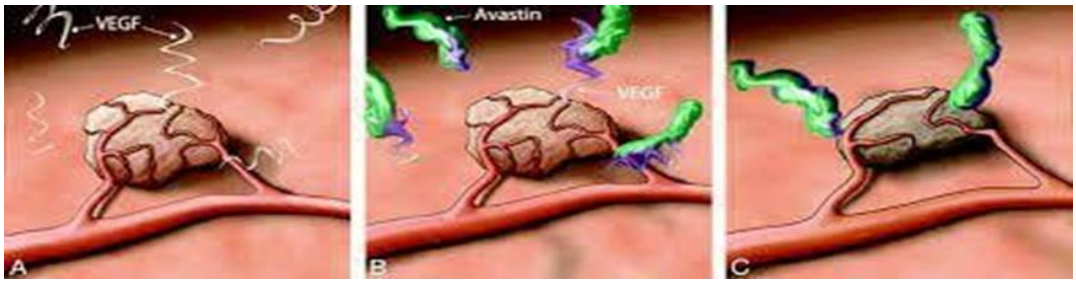

Figure 1 Bevacizumab schematic: A - Hypervascular tumor with VEGF. B - Bevacizumab binds to VEGF, reducing its concentration. C - Diminished blood supply to tumor, causing shrinkage.][2]

Vascular endothelial growth factor (VEGF) interacts with bevacizumab, a recombinant humanized monoclonal IgG1 antibody. Bevacizumab prevents VEGF from interacting withFlt1 and KDR receptors on the surface of endothelial cells, thereby inhibiting the growth ofnew blood vessels and endothelial cell proliferation.[9]

3.2. Therapeutic uses of bevacizumab

Vascular endothelial growth factor (VEGF) inhibitor Avastin (generic name: bevacizumab)is used to treat the following conditions: metastatic colorectal cancer.

Available as an injection in single-dose vials in two strengths: 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL).The injection is given intravenously (IV), which means it is put right into a vein.[10]

Guidelines for intravenous injection are as follows:Do not freeze or shake the vial and discard the unused portion. Dilute the injection solution into a total volume of 100 mL of normal saline (NS). Do not mix or dminister infusions with solutions containing glucose. If not used immediately, the diluted solution can be stored at temperatures between 2 and 8 degrees Celsius (36- and 46-degrees Fahrenheit) for up to 8 hours. Injections should be administered as an intravenous infusion only. Do not administer as an intravenous push or bolus. First, inject the injection over 90 minutes. If well tolerated, the second infusion time can beshortened to 60 minutes. Subsequent infusions he can shorten to 30 minutes, if well tolerated.[11]

Table 1 Adverse drug reactions (ADRs)

Category	**Side Effect**	**Minimum Percentage (%)**	**Maximum Percentage(%)**
Cardiovascular	Hypertension, AllGrades	19	42
Endocrine metabolic	Hyperglycemia	26	31
Endocrine metabolic	Hypomagnesemia	24	27
Endocrine metabolic	Weight decreased	11	21
Gastrointestinal	Abdominal pain	12	61
Gastrointestinal	Constipation	13	40
Gastrointestinal	Diarrhea	19	39
Gastrointestinal	Indigestion	17	24
Gastrointestinal	Loss of appetite	34	43
Gastrointestinal	Nausea	58	72
Gastrointestinal	Stomatitis	15	33
Gastrointestinal	Taste sense altered	14	21
Gastrointestinal	Vomiting	33	52
Hematologic	Hemorrhage, All Grades		
Hematologic	Neutropenia, All Grades(Cervical)	12	
Hematologic	Neutropenia, All Grades(Ovarian)	30.7	
Hematologic	Thrombocytopenia, AllGrades (Colore|	5	
Hematologic	Thrombocytopenia, AllGrades (Ovaria|	58	
Immunologic	Infectious disease (Cervical)	10	13.6
Immunologic	Infectious disease(Ovarian)	10	13.6
Immunologic	Infectious disease (Non-small cell)	10	13.6

Immunologic	Infectious disease(Glioblastoma)	55	55
Musculoskeletal	Arthralgia	28	45
Neurologic	Headache	22	49
Renal	Proteinuria, All Grades	5	20
Respiratory	Bleeding from nose	10	55
Respiratory	Dyspnea	25	30
Respiratory	Upper respiratoryinfection	40	47
Other	Fatigue	33	82

4. Discussion

The articles cover various aspects of bevacizumab: an overview of its use in various cancers, its application in neuroradiology, clinical pharmacokinetics of therapeutic monoclonal antibodies including bevacizumab, specific data on bevacizumab pharmacokinetics in solidtumors, preclinical pharmacokinetic data, aspects of early development, and the risk of heart failure in breast cancer patients treated with bevacizumab.

5. Conclusion

In conclusion, this article reviewed the pharmacokinetics, kinetics, side effects, and dose considerations of bevacizumab, an important drug administered by infusion. The pharmacokinetic properties of bevacizumab were discussed, highlighting its intravenous administration and specific dose levels available. The injection dynamics were outlined and the initial injection time was progressively shortened according to tolerance. Side effects including cardiovascular, gastrointestinal, blood, immune, musculoskeletal, nervous, renal,respiratory, and other side effects have been noted. These side effects emphasized the needfor close monitoring and prompt medical intervention. Finally, the importance of proper dosing, careful infusion, and careful monitoring to reduce the risks associated with bevacizumab was emphasized. Overall, this review provides valuable insights for health professionals in managing bevacizumab dosing and potential side effects.

Compliance with ethical standards

Acknowledgement

I'd like to thank Dr. Ronit Kumar Arvind and Dr. SP Nayak for their essential assistance and help in evaluating my work. Their knowledge, ideas, and insightful input were critical in moulding the manuscript's quality and clarity as well as to my parents and well-wishers for their constant encouragement and support during this journey. Your combined efforts have been beneficial to me. Thank you very much.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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