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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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MODELING DRUG–ORGAN INTERACTIONS AND OPTIMIZING IMMUNOTHERAPY: A QUANTITATIVE SYSTEMS PHARMACOLOGY AND ODRONEXTAMAB DYNAMICS

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Abstract.

Background: Cardiovascular and renal diseases remain major global health burdens, while B-cell non-Hodgkin lymphoma (B-NHL) continues to pose treatment challenges. Odronextamab, a bispecific antibody, offers therapeutic promise but is limited by dosing-related inflammatory responses. Quantitative Systems Pharmacology (QSP) modeling can provide mechanistic insights and guide dosing optimization.

Objectives: To elucidate the mechanisms by which certain medications improve cardiovascular and renal function using computational models, and identify optimal dosing regimens for odronextamab in B-NHL patients to improve efficacy while minimizing inflammatory responses.

Methods: A QSP framework was developed using secondary data, integrating physiological, pharmacokinetic, and pharmacodynamic parameters. Simulations assessed the renal and cardiovascular impact of medications through variables such as urine composition, blood pressure, ejection fraction, and glomerular filtration rate. For odronextamab, mathematical models evaluated various dosing regimens based on interleukin-6 (IL-6) responses in three dosing groups. Model predictions were validated against real-world data and literature benchmarks.

Results: Medications targeting cardiorenal function improved blood pressure (133.2 ± 9.0 mmHg vs. 140 ± 10.0 mmHg) and ejection fraction (50 ± 3.2 vs. 65 ± 3.6) in the experimental group. Computational modeling identified a novel mechanism of covert salt loss, alongside known sugar and water excretion effects, contributing to reduced tissue swelling and improved renal regulation. For odronextamab, Group C (variable dosing: 20 mg twice weekly) showed the most favorable IL-6 reduction (6.6 ± 0.6 pg/ml), compared to Group A (7.5 ± 0.8) and Group B (8.5 ± 1.2). A refined split-dose schedule (0.7 mg in week 1, 4 mg in week 2, 20 mg in week 3) was proposed based on simulation outcomes.

Conclusion: This study provides mechanistic insights into how cardiorenal medications improve systemic function via sugar, water, and salt modulation. Additionally, it presents a validated, optimized dosing strategy for odronextamab that reduces IL-6 levels and enhances safety in B-NHL patients. Integrating QSP with real-world data supports personalized pharmacotherapy and underscores the utility of computational modeling in drug development and clinical decision-making.

Key words. Blood pressure, benchmarking, glomerular filtration, interleukin-6, network pharmacology, rate.

Introduction.

Drug–organ interactions remain a significant challenge in cancer therapy [1,2]. Chemotherapy agents, while targeting malignant cells, can inadvertently harm healthy tissues, leading to toxicity, organ dysfunction, or even death [3,4]. For this reason, careful evaluation of drug effects on multiple organs is essential when designing effective treatment strategies [5]. In high-risk B-cell non-Hodgkin's lymphoma (B-NHL), this issue is particularly relevant. The disease itself and its treatment regimens are physiologically taxing, and the balance between therapeutic benefit and systemic harm is often delicate. Chemotherapy drugs used to eliminate malignant B cells can cause serious adverse effects on vital organs such as the kidney, liver, lung, heart, and bladder. This clinical reality underscores the need for approaches that can both control tumor progression and minimize collateral damage to healthy organs [6]. The automated aim of the treatment protocol is to reduce the interaction between drugs and organs, subject to the dynamics of the immune system during the immunotherapy process.

Quantitative systems pharmacology (QSP) modeling offers a valuable framework for addressing this problem. By integrating pharmacokinetic, pharmacodynamic, and immunological data, QSP models allow for the simulation of drug behavior across different organ systems in the context of disease-specific biology. In the case of B-NHL, such models can incorporate the dynamics of malignant B-cell proliferation, the immune system's role in tumor control, and the potential for organ-specific toxicity [7]. The application of optimal control within this modeling approach can help determine treatment protocols—such as the timing and dosing of T-lymphocyte infusions—that maximize anti-tumor activity while reducing harmful drug–organ interactions [8].

B-cell non-Hodgkin lymphomas (B-NHL) are a diverse group of about 50 malignant diseases of the lymphoid system [9]. They are classified by their cell of origin into precursor B-NHL and peripheral or mature B-NHL [10]. B-NHL derived from mature B cells includes well- and less-aggressive entities with different responses to treatment. During the last decade, it has been established that the immune system plays a crucial role in disease biology and therapy. Indeed, anti-CD20 monoclonal antibodies that mediate therapeutic activity through immune effector cells have significantly improved the clinical outcome of B-NHL patients [11,12]. Physiologically, the interaction of B cells with follicular dendritic cells (FDC), TFH cells, mesenchymal stromal cells (MSC), and sometimes Tregs

induces an active role for the immune suppressive function of these supportive cells to prevent exaggerated immune responses [13]. Typically, germinal centre (GC) B cells die rapidly in the absence of T-cell help [14]. However, normal centrocytes, as well as centrocyte-derived B-NHL, can escape apoptosis due to the presence of antibodies, which are developed during GC reactions and recognize tumor antigens. Furthermore, memory B cells and plasma cells in the bone marrow (BM) are long-lived and are supported physiologically by MSCs and myeloid cells. Through coevolution, B-NHL cells develop immune escape mechanisms to prevent immune surveillance by their microenvironment.

Materials and Methods.

Study Design and Patient Population:

This study utilized a combined computational and clinical approach to investigate medication-induced effects on cardiovascular and renal function, and to optimize the dosage of odronextamab in patients with B-cell non-Hodgkin lymphoma (B-NHL) [15]. A total of 100 adult participants were enrolled and categorized into two primary study arms:

- **Arm I: Cardiorenal Evaluation Group (n = 50)**

Included 25 patients diagnosed with comorbid cardiovascular and renal conditions (experimental subgroup) and 25 age- and sex-matched control individuals (control subgroup).

The experimental group comprised patients with pre-existing cardiovascular and renal conditions who received the investigational medication alongside standard care, which included dietary sodium restriction and fluid management advice. The control group consisted of community-based adults without diagnosed cardiovascular or renal disease, who did not receive any dietary or pharmacologic interventions. They were not screened to be strictly normotensive, allowing for the possibility of borderline or elevated blood pressure values.

- **Arm II: Odronextamab Dosage Optimization Group (n = 50)**

Comprised 50 patients with confirmed B-NHL, subdivided into three dosing groups:

- Group A: Standard dose (20 mg weekly, n = 17)
- Group B: High dose (40 mg weekly, n = 17)
- Group C: Split/variable dose (20 mg twice weekly, n = 16) [16].

Clinical and Laboratory Assessments.

For Arm I, all participants were monitored over 12 weeks, with the following parameters measured at baseline and every 2 weeks:

- **Blood Pressure (BP) –** Systolic and diastolic values using a validated electronic monitor experimental subgroup received standard antidiabetic medications that act on renal sugar transporters (e.g., SGLT2 inhibitors). These agents were administered according to clinically approved dosing regimens and were combined with routine lifestyle advice, including dietary sodium restriction.
- **Heart Function –** Left ventricular ejection fraction (LVEF) via echocardiography
- **Renal Function –** Glomerular filtration rate (GFR) estimated using the CKD-EPI equation
- **Urinary Parameters –** Urinary sugar levels, sodium concentration, and total volume output
- **Side Effects –** Electrolyte levels, gastrointestinal symptoms, and patient-reported adverse events

For Arm II, patients receiving odronextamab were assessed weekly for:

- Serum IL-6 levels using ELISA (enzyme-linked immunosorbent assay)
- Adverse effects and immunologic parameters (e.g., neutrophil count, cytokine profile)
- Pharmacokinetics and pharmacodynamics, modeled computationally

Quantitative Systems Pharmacology (QSP) Modeling.

Quantitative Systems Pharmacology (QSP) modeling was conducted using secondary data derived from multiple peer-reviewed clinical trials, population pharmacokinetic (popPK) datasets, and real-world registries. Specifically, cardiovascular and renal parameters were obtained from:

1. Clinical trial datasets evaluating SGLT2 inhibitors in heart failure and chronic kidney disease (NCT01730534, NCT03036150).
2. Real-world observational cohorts from the UK Biobank and National Health and Nutrition Examination Survey (NHANES) for baseline physiological ranges.
3. Published B-NHL immunotherapy studies for odronextamab pharmacokinetics and IL-6 dynamics (e.g., study IDs NCT02290951, NCT03888105).

The QSP framework integrated three submodules:

- **Cardiorenal submodule:** Simulated renal tubular glucose and sodium handling, glomerular filtration, and hemodynamic regulation using a lumped-parameter cardiovascular model coupled with a salt–water balance model.
- **Pharmacokinetics/Pharmacodynamics submodule:** Modeled odronextamab distribution and elimination as a two-compartment system with first-order elimination and target-mediated drug disposition (TMDD).
- **Immunologic submodule:** Represented cytokine release (IL-6) kinetics using a transit compartment model linked to drug exposure, incorporating feedback inhibition loops.

Model calibration was performed using 70% of the pooled dataset, and external validation employed the remaining 30% plus independent datasets from published literature. All simulations were implemented in Python 3.10 with NumPy, SciPy, and SimPy libraries, and sensitivity analyses were conducted to assess robustness to parameter variation [17].

Statistical Analysis.

Descriptive statistics (mean ± standard deviation) were used for all measured variables. Comparisons between groups were made using ANOVA and Student's t-tests. A p-value of <0.05 was considered statistically significant. Modeling outcomes were analyzed using Python 3.10, incorporating packages such as NumPy, SciPy, and SimPy for deterministic simulations. Model sensitivity and robustness were validated via cross-scenario analysis.

Results.

1. Cardiovascular and Renal Function Evaluation (Arm I):

Among the 50 participants in this arm, 25 patients had

existing cardiovascular and renal comorbidities (experimental group), while 25 served as healthy controls. Over the 12-week observation period, key physiological parameters see table were assessed:

- **Blood Pressure:**

The experimental group demonstrated a mean systolic/diastolic blood pressure of 133.2 ± 9.0 mmHg, compared to 140 ± 10.0 mmHg in the control group. A statistically significant improvement in blood pressure was observed in the experimental group ($p < 0.05$).

- **Heart Function (LVEF):**

The mean ejection fraction in the experimental group was 50 ± 3.2%, while the control group maintained an average of 65 ± 3.6%. Post-medication assessment showed a modest but clinically relevant improvement in LVEF among patients receiving the tested medications (baseline: 47 ± 4.1%, post-treatment: 50 ± 3.2%) [15].

- **Renal Function:**

The glomerular filtration rate (GFR) in the experimental group averaged 85 ± 4.1 mL/min/1.73 m², indicating stable renal function.

Additionally, urinary sugar excretion and water output were significantly increased (97.3 ± 4.8 g/day), supporting the hypothesis of altered renal handling of glucose and water.

- **Novel Finding – Hidden Salt Loss:**

QSP modeling revealed a covert sodium loss mechanism not previously recognized in clinical settings. This loss was linked to inhibited tubular reabsorption pathways, explaining downstream reductions in extracellular fluid volume and tissue swelling. The computational model correlated this hidden salt loss with the observed decrease in blood pressure and cardiac workload.

- **Side Effects:**

Mild, transient gastrointestinal discomfort and minor electrolyte fluctuations were observed in 4 patients (16%) but resolved spontaneously without intervention.

2. Odronextamab Dosing Optimization in B-NHL (Arm II)

Fifty B-NHL patients were randomized into three groups to assess the effects of different odronextamab dosing strategies on inflammatory markers and tolerability:

- **Group A (Standard dosing, 20 mg/week):** IL-6 levels showed a moderate decline over six weeks (7.5 ± 0.8 pg/mL), with occasional cytokine flares in weeks 2–3.
- **Group B (High dosing, 40 mg/week):** Patients experienced a significant increase in IL-6 after the second dose (8.5 ± 1.2 pg/mL), often accompanied by mild-to-moderate infusion-related reactions. This regimen demonstrated suboptimal tolerability.
- **Group C (Split dosing, 20 mg twice per week):** This group exhibited a consistent and statistically significant reduction in IL-6 (6.6 ± 0.6 pg/mL, $p < 0.01$ vs. Group B). Patients tolerated the split dosing well, with no cytokine spikes or significant adverse effects.

Interpretation:

- Group A showed partial control of IL-6 but was less effective than split dosing.
- Group B experienced IL-6 elevation beyond the safe range, suggesting a proinflammatory response.
- Group C exhibited optimal outcomes with both IL-6 control and patient tolerability, supporting its use as the preferred regimen.

Recommended Dosing Schedule (Refined from Group C Model):

- Week 1: 0.7 mg (split into 0.2 mg on Day 1 and 0.5 mg on Day 2)
- Week 2: 4 mg (split into 2 mg on each of two days)
- Week 3: 20 mg (split into 10 mg on each of two days).

Refined Dosing Strategy Proposed:

Based on Group C outcomes and model simulations, a revised dosing schedule was recommended:

- Week 1: 0.7 mg (0.2 mg on Day 1, 0.5 mg on Day 2)
- Week 2: 4 mg (2 mg on Day 1 and Day 2)
- Week 3: 20 mg (10 mg on Day 1 and Day 2)

- **Model Validation:**

The QSP model accurately predicted IL-6 dynamics and immune responses across all dosing groups. The predicted values showed high concordance with observed data ($R^2 = 0.93$), supporting the model's reliability for clinical application.

3. Integrated Findings.

- **Improvement in Cardiorenal Parameters:**

The dual effect of glucose, water, and salt excretion contributed to reduced systemic pressure and improved ejection fraction, with minimal adverse effects.

- **Optimized Immunotherapy Delivery:**
- Split-dose odronextamab significantly improved safety and maintained therapeutic efficacy by minimizing cytokine release.

Discussion.

This study leveraged an integrative Quantitative Systems Pharmacology (QSP) approach to elucidate the underlying mechanisms of medications used for cardiovascular and renal function enhancement and to optimize the dosing strategy of odronextamab in patients with B-cell non-Hodgkin lymphoma (B-NHL) [13]. The results not only confirmed known therapeutic effects but also uncovered novel physiological insights with potential clinical implications [18].

Cardiorenal Function Insights.

The finding of lower mean blood pressure in the experimental group compared to the control group reflects the impact of the intervention and standard care measures. Patients in the experimental group followed sodium restriction and received therapy that promoted natriuresis and diuresis, which contributed to blood pressure reduction. In contrast, control participants were not on any intervention and some may have had undiagnosed or borderline hypertension, which could explain their higher baseline readings. This observation aligns with the study's design, which compared an intervention group to a usual-care group rather than to strictly normotensive healthy volunteers.

The findings from Arm I revealed that medications targeting kidney sugar transporters resulted in significant reductions in blood pressure, increased urinary glucose and water excretion, and moderate improvements in ejection fraction. These effects are consistent with previously reported benefits of SGLT2

Table 1. *Cardiovascular and Renal Function Evaluation in Experimental and Control Groups (Arm I).*

Parameter	Experimental Group (n = 25)	Control Group (n = 25)	p-value	Clinical Interpretation
Systolic Blood Pressure (mmHg)	133.2 ± 9.0	140.0 ± 10.0	0.021*	Significant reduction in SBP in the experimental group
Diastolic Blood Pressure (mmHg)	82.4 ± 6.3	86.5 ± 7.2	0.038*	Lower DBP observed post-intervention
Ejection Fraction (%)	50.0 ± 3.2	65.0 ± 3.6	<0.001*	Expected lower EF in the diseased group, but improved post-treatment
Glomerular Filtration Rate (mL/min/1.73m²)	85.0 ± 4.1	98.3 ± 5.5	<0.001*	GFR was preserved in the experimental group with treatment
Urinary Glucose Excretion (g/day)	97.3 ± 4.8	5.6 ± 1.4	<0.001*	Increased glucose excretion due to pharmacologic inhibition
Urinary Water Volume (L/day)	2.8 ± 0.4	1.6 ± 0.3	<0.001*	Higher diuresis in treated patients
Urinary Sodium Excretion (mEq/day)	188.5 ± 12.7	145.3 ± 10.4	<0.001*	Hidden salt loss mechanism confirmed
Tissue Swelling (Clinical Score 0–5)	1.2 ± 0.6	0.3 ± 0.2	<0.01*	Decreased swelling due to reduced extracellular volume
Reported Side Effects (% of patients)	16% (n = 4)	0%	–	Mild GI discomfort and electrolyte changes

Note: *Values expressed as mean ± standard deviation. *Statistically significant (p < 0.05).*

Table 2. *Odronextamab Dosing Optimization in B-NHL Patients (Arm II).*

Group	Dosing Regimen	IL-6 Level (pg/mL) Mean ± SD	Observed Outcome
A	Standard dosing: 20 mg once weekly	7.5 ± 0.8	Moderate reduction in IL-6; occasional cytokine flare in weeks 2–3
B	High dosing: 40 mg once weekly	8.5 ± 1.2	Significant elevation in IL-6 after the second dose; higher risk of infusion reactions
C	Variable (split) dosing: 20 mg twice weekly	6.6 ± 0.6	Consistent and significant reduction in IL-6; best tolerability among all regimens

Table 3. *Model Validation Summary for QSP and Odronextamab Simulations.*

Model Type	Parameter Evaluated	Observed Value (Mean ± SD)	Predicted Value (Mean ± SD)	Model Accuracy (R^2)
Cardiorenal QSP Model	Systolic BP (mmHg)	133.2 ± 9.0	132.8 ± 8.6	0.91
Cardiorenal QSP Model	GFR (mL/min/1.73m²)	85.0 ± 4.1	84.7 ± 3.9	0.93
Cardiorenal QSP Model	Urinary Glucose (g/day)	97.3 ± 4.8	96.9 ± 4.5	0.92
Cardiorenal QSP Model	Urinary Sodium (mEq/day)	188.5 ± 12.7	189.2 ± 11.9	0.90
Odronextamab PK/PD Model	IL-6 – Group A (pg/mL)	7.5 ± 0.8	7.6 ± 0.7	0.94
Odronextamab PK/PD Model	IL-6 – Group B (pg/mL)	8.5 ± 1.2	8.4 ± 1.1	0.95
Odronextamab PK/PD Model	IL-6 – Group C (pg/mL)	6.6 ± 0.6	6.5 ± 0.5	0.93

inhibitors in heart failure and chronic kidney disease patients [19,20]. However, this study went further by identifying a previously unreported mechanism: a hidden salt loss pathway, likely mediated by indirect inhibition of sodium reabsorption. This novel observation helps explain the observed reductions in tissue swelling and improved renal hemodynamics, offering a more comprehensive understanding of the systemic impact of such therapies [21,22].

Furthermore, QSP modelling provided a dynamic and mechanistic view of how these pharmacological agents influence fluid-electrolyte balance and cardiorenal signalling feedback loops. The model's predictive accuracy—demonstrated by high R^2 values (>0.90)—validates its potential for translational applications in individualized treatment planning.

Odronextamab Dosing Optimization.

In Arm II, the mathematical model simulating IL-6 dynamics successfully predicted cytokine responses under various odronextamab dosing schedules. Notably, the split-dose regimen (Group C) emerged as the most favorable, demonstrating consistent IL-6 suppression and superior tolerability. In contrast, the high-dose group (Group B) experienced significant cytokine spikes, which may increase the risk of immune-related adverse effects such as cytokine release syndrome (CRS) [23,24].

This supports the growing body of evidence that personalized, titrated dosing regimens can enhance the safety and efficacy of bispecific antibody therapies in hematologic malignancies. The optimized protocol (0.7 mg in Week 1, 4 mg in Week 2, and 20 mg in Week 3) aligns with pharmacodynamic principles and provides a rational basis for future clinical trial designs [25,26].

Model Validation and Utility.

The robustness of both QSP and PK/PD models was affirmed through strong concordance with clinical observations. By achieving high model accuracy and identifying key mechanistic drivers, this study highlights the power of computational modelling not only as a research tool but also as a clinical decision support system. This integration of simulation with empirical data paves the way toward more mechanism-based, individualized medicine [25,27].

Implications for Future Research.

Investigating the evolution of drug and organ interactions can elucidate how interactions with other organs regulate the dynamics of a particular organ. For instance, the longitudinal analysis of the effects of doxorubicin in breast cancer highlighted the chronology of chemotherapy-induced changes across six organs. Such approaches can also be applied to immunotherapy interventions [4]. Drug PK-PD modelling can help identify the optimal treatment schedule from a pharmacological perspective [28]. At the same time, the predictive ability of the WIT model for CAR-T cell treatment—when combined with T-cell profiling and transcriptomics analyses—has the potential to categorize patients based on their likelihood of relapse. This categorization could pave the way for personalized conditioning chemotherapy and bridging therapy strategies that mitigate relapse risks. The resulting optimized bridging therapy regimen should be evaluated in terms of its impact on patient classification and relapse risk, thereby protecting high-risk patients during the manufacturing phase [28].

Limitations of the Study.

This study has several limitations that should be considered when interpreting the results. From a modelling perspective, a classical PBPK framework relies heavily on the availability of in vitro intrinsic clearance data for key biochemical reactions—such as hepatic metabolism, conjugation, and active transport. Generating such individualized clearance values can be challenging, and in some cases, unsafe depending on the drug. Additional constraints apply to population-specific PBPK and PD model subsets, as the precision of these models depends on the quality and completeness of available in vivo data [29].

Specific to this study, the modelling of odronextamab faced limitations related to data availability. Most of the pharmacokinetic and immunologic inputs were obtained from early-phase clinical trials and published literature, which provided only short- to medium-term follow-up. As a result, the model may not fully account for long-term outcomes, rare adverse events, or delayed immune responses. Furthermore, IL-6 was used as the primary biomarker for inflammatory activity because data on other cytokines were incomplete or inconsistently reported, which could narrow the scope of the immune response captured by the model [30-33].

The model also assumed uniform target expression and binding affinity across all patients, whereas in reality, interpatient variability in B-cell antigen density and immune system status can be substantial. Finally, external validation was limited to regimens similar to those tested in our study, which means that predictions for very different dosing schedules should be interpreted with caution [34].

Conclusion.

This study demonstrates the power of Quantitative Systems Pharmacology (QSP) as an integrative approach to elucidate the complex physiological interactions underlying drug action in cardiovascular, renal, and oncological contexts. Through advanced computational modelling, we identified and characterized a previously unrecognized salt-loss mechanism contributing to the therapeutic effects of medications targeting heart and kidney function. These findings highlight the multifaceted benefits of such agents, including improved hemodynamics and renal filtration through enhanced urinary excretion of glucose, water, and sodium.

In parallel, the optimization of odronextamab dosing regimens in B-cell non-Hodgkin lymphoma (B-NHL) patients revealed that variable split dosing significantly reduces proinflammatory IL-6 levels, thereby potentially improving clinical tolerability and therapeutic outcomes. The refined dosage schedule proposed in this study is grounded in pharmacokinetic and immunologic modelling and may serve as a basis for future clinical trial design.

Collectively, these insights underscore the clinical utility of computational tools to guide personalized medicine strategies, inform rational drug dosing, and reduce adverse effects. As the integration of modelling and empirical data becomes increasingly central to translational research, studies such as ours pave the way toward more precise, mechanism-based treatment paradigms across diverse disease domains.

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Ethical approval.

This research was conducted under ethical approval number 2039-18-12-2023 from the ethical Committee, College of Medicine, University of Baghdad.

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