ANNOTATION

of the dissertation work of doctoral student Akerke Auanassova on the topic **«Systemic vasculitis at the present stage: clinical and laboratory characteristics and optimisation of patient management strategy»**, submitted for the degree of Doctor of Philosophy (PhD) on speciality 8D10141 «Medicine»

Relevance of the research topic

The relevance of this dissertation research is due to several factors reflecting current pressing health problems. The incidence of primary systemic vasculitis (SV) worldwide is more than 100 cases (per 1 million) (Watts et al., 2008), although the prevalence of the disease varies depending on the type of SV and geographical location (Dreyer et al., 2011; Gudbrandsson et al., 2017; Romero-Gómez et al., 2015; Watts et al., 2009; Watts et al., 2000; Sacri et al., 2015).

SV is considered a problem that causes several problems from the point of view of diagnosis and treatment. Diagnosis of systemic vasculitis is a difficult task due to the rarity and complexity of the clinical picture (multiorgan lesion), which can lead to late treatment causing damage to target organs, disability, mortality and increased financial costs for additional studies, which also include non-essential tests (Prior et al., 2017, Taimen et al., 2021).

In worldwide studies, the level of disability associated with the diagnosis of SV is about 20-30% (Mau et al., 2005; Reinhold-Keller et al., 2002). Recent studies have shown that disability still negatively affects 20-40% of patients with SV (Barra et al., 2016; Basu et al., 2014; Benarous et al., 2017).

Studies that examined the financial consequences of early retirement or disability due to a diagnosis of SV found that income decreased significantly in 5-26% of patients (Benarous et al., 2017; Abdou et al., 2002).

The purpose of the dissertation research

Optimising the treatment tactics (management) and identification of patients with systemic vasculitis in the Republic of Kazakhstan at the present stage, considering clinical and laboratory data.

Objectives of the research work:

1. To analyse SV that first appeared after infection with COVID-19 (SARS-CoV-2) and vaccination (according to the literature);
2. To evaluate the factors leading to delayed diagnosis of SV;
3. To study the demographic, clinical and anamnestic characteristics of patients with B in the period from 2019 to 2021 for SV;

4. To assess the knowledge and perceptions of healthcare professionals of the Republic of Kazakhstan and foreign countries on SV;
5. To develop recommendations for optimising the management strategy of patients with SV.

Research methods

1. Analytical study (analysis of systemic vasculitis that first appeared after infection with COVID-19 (SARS-CoV-2) and vaccination; analysis of the causes, consequences and results of delayed diagnosis of explosives);
2. Retrospective study (analysis of the medical history of 162 patients);
3. Cross-sectional study (development, dissemination and interpretation of the questionnaire).

Statistical methods (statistical and mathematical data processing was carried out using the SPSS application software package version 20.0 (IBM).

The object of the study

The object of the study is patients with a verified diagnosis of SV. Inclusion criteria: patients with a verified diagnosis of SV over 18. Exclusion criteria: patients under the age of 18, with pregnancy, cancer, neurological diseases, mental disorders, symptoms of psychotropic drug poisoning and alcoholism.

The subject of the study

The dissertation research subjects are the demographic and clinical anamnestic characteristics of patients with SV, the factors leading to a delay in the diagnosis of SV, and the knowledge and understanding of healthcare professionals regarding SV.

Provisions to be defended

1. SV is most often found in women of reproductive age in the studied population. Takayasu's disease and IgA vasculitis were the most common. The most common clinical symptoms in patients with SV were injuries to the musculoskeletal system, gastrointestinal tract, skin, peripheral vessels and cardiovascular system.
2. The study revealed a heterogeneity in how treating physicians identify and approach the management of ANCA-associated vasculitis (AAV). There is a lack of consensus regarding diagnosing and treating AAV during COVID-19 (SARS-CoV-2). However, all respondents were united in stating the need to improve their knowledge of AAV during medical training.
3. Based on the results of PCR testing, recommendations have been developed for managing SV patients during and after vaccination against COVID-19 (SARS-CoV-2).

The results of the study are presented in the form of a series of articles (7 publications)

1. **SARS-CoV-2 as a trigger of IgA vasculitis: a clinical case and literature review («Rheumatology International», Германия; Q2 по данным Journal Citation Reports (Clarivate Analytics); the first author, the corresponding author);**
2. **New-onset systemic vasculitis following SARS-CoV-2 infection and vaccination: the trigger, phenotype, and outcome («Clinical Rheumatology», Great Britain; Q3 according to the Journal Citation Reports (Clarivate Analytics).**

   SARS-CoV-2 and COVID-19 vaccines can potentially cause systemic vasculitis, similar in phenotype to primary vasculitis. IgA vasculitis is the most common form of vasculitis reported after infection with COVID-19 or after vaccination. Viral-induced vasculitis has a better prognosis than systemic vasculitis de novo, with a favourable response to systemic corticosteroids with or without immunosuppression. Steroids play a central role in treatment, and in most reported cases, a positive effect was observed when taking prednisone at a dose of 0.8 to 1 mg/kg/day. The need for pulse therapy with methylprednisolone and additional cytotoxic and immunosuppressive therapy should be determined individually, depending on the damage to the main organs and the disease progression rate. Patients receiving B-cell-destroying therapy, mainly patients with pre-existing AAV, have a reduced immunogenic response to the vaccine. Therefore, they may be more susceptible to developing a more severe COVID-19 phenotype.
3. **Diagnostic delays in systemic vasculitis: The causes, implications and outcome («Rheumatology International», Germany; Q2 according to the Journal Citation Reports (Clarivate Analytics); the first author).**

   The relatively low incidence, lack of awareness among general practitioners, and heterogeneity of clinical manifestations indicate a delay in diagnosing systemic vasculitis. The time from the beginning to the final diagnosis of Takayasu's disease and granulomatosis with polyangiitis (GPA) is 4.9 (months) and 4.16 (months), respectively; the difference is unreliable. It takes 11.3% longer to diagnose IgA vasculitis than Takayasu's disease.

   The diagnosis of Behcet's disease is the most problematic and time-consuming, and diagnosis takes 53% more time than Takayasu's disease. Increased awareness of therapists and equal and timely access to specialized rheumatology care can ensure the initiation of urgent, definitive treatment, which will lead to reduced damage and improved quality of life with improved long-term results. It is essential to raise awareness among the general public and practitioners about the early detection of vasculitis and the introduction of effective referral systems with prompt access to research resources such as ultrasound. Achieving this goal requires the active

participation and consent of all stakeholders, including individual rheumatologists, various medical societies, and politicians.

4. **The impact of the COVID-19 pandemic on patients with systemic vasculitis: a single-centre retrospective study («Rheumatology International», Germany; Q2 according to the Journal Citation Reports (Clarivate Analytics); the first author, the corresponding author).**

   A single-centre retrospective study of the medical records of 82 patients hospitalized with systemic vasculitis from January 2019 to December 2021 was conducted at the Regional Clinical Hospital. The following qualitative (gender, disability, concomitant diseases) and quantitative (age, length of illness, laboratory data, etc.) variables were studied. According to the study results, there is a decrease in the number of hospitalized patients with vasculitis in the rheumatology department of the regional clinical hospital in the study population. Compared to 2019, the number of hospitalized patients has almost halved in 2021. Of the 82 cases, the most common were Takayasu disease (nonspecific aortoarteritis) (43.9%), IgA vasculitis (Schoenlein-Henoch disease) (31.71%), and they are characteristic mainly of women of rural origin who were admitted to the hospital in a concomitant condition ($p<0.001$). 41.6% of patients have a disability. Moreover, most patients have group II disability. The average body mass index is 24.2; 27 patients out of the total number of patients are obese. The most common clinical symptoms in patients with systemic vasculitis were injuries to the musculoskeletal system (75.6%). An average negative correlation was found between the indicators of the level of ESR and haemoglobin; the correlation coefficient was -0.535. The patients had concomitant diseases such as diabetes mellitus, iron deficiency anaemia, coronary heart disease, hypertension, gastrointestinal tract diseases and hepatitis. The high level of disability identified among patients can be explained by two main factors: firstly, the fact that patients did not consult doctors promptly, and secondly, the fact that the medical community is insufficiently informed about the treatment of autoimmune rheumatic diseases, in particular about systemic vasculitis, which makes timely diagnosis and treatment especially difficult. The patients included in this study mainly suffered from diseases of the musculoskeletal system, but depending on the type of vasculitis, other organs and systems may be affected.

5. **Clinical and anamnestic features of patients with systemic vasculitis: a single-centre retrospective study («Rheumatology International», Germany; Q2 according to the Journal Citation Reports (Clarivate Analytics); the first author, the corresponding author).**

   A single-centre retrospective study of medical records of 80 patients over 18 was conducted at the city Rheumatology centre. The medical records of 24 men (30%) and 56 women (70%) with systemic vasculitis diagnosed between January 2019 and

December 2021 were analyzed. Of the 80 patients registered in 2019-2021, the most common were patients with IgA vasculitis (n=32, 40%), Takayasu arteritis (n=17, 21.25%) and granulomatosis with polyangiitis (n=12, 15%). Behcet's disease was diagnosed less frequently (n=9, 11.25%). Nineteen patients with systemic vasculitis had pre-obesity, grade I obesity (n=13) and grade II obesity (n=2). Musculoskeletal system disorders were observed in 52 patients (65%). Disorders of the gastrointestinal tract, skin and cardiovascular system have been reported in 45 (56,3%), 37 (46,3%), and 39 (48.8%) patients, respectively. Only eight patients (10%) had lesions of the nervous system. Most patients had elevated C-reactive protein levels (29 people, 36.3%) and leukocytosis (33 people, 41.3%). A third of the patients with vasculitis had a history of abortions.

6. **Physicians' perceptions about antineutrophil cytoplasmic antibody-associated vasculitis (AAV): an online survey report in the time of the COVID-19 pandemic» («Clinical Rheumatology», Great Britain; Q3 according to the Journal Citation Reports (Clarivate Analytics); the first author).**
   An online questionnaire containing 28 questions was conducted based on relevant international practice guidelines, recommendations and previous online surveys on AAV. Only completed questionnaires were analyzed using descriptive statistics. A total of 113 respondents from 21 countries responded, among whom rheumatologists (63.7%), internists (12.4%) and general practitioners (7.08%) were the most common. The top five countries are Turkey (24), Kazakhstan (22), India (10), Ukraine (8) and Croatia (8). Forty-five (40%) worked in clinics specializing in treating patients with AAV. They commented on the organs involved in AAV, vasculitis secondary to infections, medications, or other rheumatic diseases, various tests useful for diagnosing AAV, and the choice of drugs for induction and maintenance. The respondents spoke about their experience in treating COVID-19 in patients with AAV and about the vasculitis manifestations of COVID-19. Various methods of reducing cardiovascular risks in AAV have been mentioned. Respondents indicated that medical education must be strengthened to increase awareness and knowledge about AAV. This survey helped to gain information about the differences in the perception of AAV in different countries, including current practices and recent management changes. It also provided information on the treatment of COVID-19 in patients with AAV. This study showed that there is still a need to understand standard definitions, and there is a gap between the guidelines and current practice.
7. **The fifth task of the study was completed by developing recommendations on the topic: «Recommendations for the management of systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2)».** The recommendations are based on the clinical protocols of the Republic of Kazakhstan, the recommendations of EULAR (European League Against

Rheumatism), ACR (American College of Rheumatology), the literature data of recent years and the results of own research. The guidelines have been developed as a guide for medical professionals providing medical care to patients with autoimmune rheumatological diseases, students and residents of medical universities.

The scientific novelty of the research work

1. In the Republic of Kazakhstan (2019-2021), the types and features of SV that are most common among the adult population in modern conditions, depending on gender, age, and socio-demographic characteristics, were studied;
2. Recommendations have been developed for SV in COVID-19 (SARS-CoV-2) and after COVID-19 (SARS-CoV-2)vaccination;
3. For the first time, a survey on SV (AAV) was conducted among healthcare professionals of the Republic of Kazakhstan and foreign countries, and physicians' knowledge and perceptions regarding SV were evaluated.

The practical significance of the results

The theoretical provisions and practical results of this dissertational work, in particular «Recommendations for the management of systemic vasculitis during COVID-19 and after vaccination against COVID-19», are included in the educational process and research work of the bases of the Department of Therapy and Cardiology of the South Kazakhstan Medical Academy (act of implementation, 2023), and also in the clinical work of the clinics «Alinur and K» (act of implementation, 2024) and «Student polyclinic» (act of implementation, 2024) in Shymkent.

At the same time, as a result of the dissertation work, two author's certificates were obtained: «Questionnaire for assessing the understanding of doctors of the management of vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) (AAV) in COVID-19»,№38061 dated July 21, 2023 and «Recommendations for the management of systemic vasculitis during COVID-19 and after vaccination against COVID-19», №39155 dated September 21, 2023.

A questionnaire to assess doctors' understanding of managing antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) in COVID-19 (SARS-CoV-2) can be used to study other rheumatological diseases.

According to the Scopus database, scientific articles with the results of this study have been cited in more than 20 international scientific papers.

Personal contribution of a doctoral student

The author of the dissertation conducted a literary review of modern databases such as Scopus, WoS, and PubMed/MEDLINE on the problems of systemic vasculitis. Based on the identified problem, the purpose and objectives of scientific research were formulated, the study's design was selected, and the research object was determined. The author personally completed all the planned tasks, including the organization of research, collection and analysis of initial data, and formed the

appropriate conclusions. The dissertation's author created, piloted and disseminated an international online questionnaire for medical professionals. The doctoral student has written and published several publications on dissertation research. The doctoral student is the first and corresponding author in most published articles. In addition, the author of the dissertation has developed «Recommendations for the treatment of systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2)».

Conclusions

1. Literature data show that COVID-19 (SARS-CoV-2) infection and COVID-19 (SARS-CoV-2) vaccines can cause SV similar to the phenotypes of primary vasculitis. IgA vasculitis and leukoclastic skin vasculitis are the most common vasculitis reported after infection or vaccination with COVID-19 (SARS-CoV-2), with a better prognosis than de novo vasculitis. Steroids play a central role in treatment, and in most reported cases, a positive effect of prednisone doses of 0.8 to 1 mg/kg per day was observed. Vasculitis that developed after COVID-19 (SARS-CoV-2) damages blood vessels of all sizes, and therefore, it was recommended that they be classified as «Virus-specific vasculitis» in the Chapel Hill consensus.
2. The relatively low level of SV, the lack of awareness of general practitioners, and the uneven clinical signs of CB suggest a delay in diagnosis. The time from the beginning to the final diagnosis of Takayasu's disease and Granulomatosis with polyangiitis (GPA) is 4.9 (months) and 4.16 (months), respectively; the difference is unreliable. It takes 11.3% longer to diagnose IgA vasculitis than Takayasu's disease. The diagnosis of Behcet's disease is the most problematic and time-consuming, and diagnosis takes 53% more time than Takayasu's disease.
3. A retrospective study of the demographic, clinical, and anamnestic characteristics of patients with SV in 2019, 2020, and 2021 showed that SV is most often found in women of reproductive age in the studied population. Takayasu disease (nonspecific aortoarteritis) (43.9%) and IgA vasculitis (Schonlein-Henoch disease) (31.71%) were the most common.
4. The patients had concomitant diseases such as diabetes mellitus, iron deficiency anaemia, coronary heart disease, hypertension and diseases of the gastrointestinal tract. In the studied groups, 27.1% of patients have a disability, and the majority of patients have group II disability. Of the 162 patients, 37.6% are obese. The most common clinical symptoms in patients with SV were injuries to the musculoskeletal system (75.6%), digestive system (57.3%), skin (48.8%), peripheral vessels (37.8%) and cardiovascular system (31.7%).
5. A cross-sectional analysis (online survey) among healthcare professionals revealed heterogeneity in the diagnosis and treatment of AAV. There is no consensus on patient management during COVID-19 (SARS-CoV-2). However, the respondents came to a common conclusion about the need to raise awareness of AAV during medical education.
6. «Recommendations for managing systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2)» were developed.

The recommendations are based on the clinical protocols of the Republic of Kazakhstan, the recommendations of EULAR (European League Against Rheumatism), ACR (American College of Rheumatology), as well as the literature data of recent years and the results of individual studies. The guidelines have been developed as a guide for medical professionals providing medical care to patients with autoimmune rheumatological diseases, students and residents of medical universities.

Approbation of the research results

The materials of the scientific research were presented at conferences:

1. The 75th International Scientific and Practical Conference of Medical Students and Young Scientists "Modern Medicine and Pharmacy: New Approaches and Current Research", **Republic of Uzbekistan, Samarkand** 2021 y., May 18;
2. «COVID-19 and other topical infections in Central Asia» International Scientific and Practical Conference, **Republic of Kazakhstan, Shymkent**, 2022;
3. International scientific and practical conference «Medicine of Tomorrow: the scientific legacy of Academician M. A. Aliyev», dedicated to the 90th anniversary of Academician M. A. Aliyev and the 30th anniversary of the Kazakh-Russian Medical University, **Republic of Kazakhstan, Almaty**, 2023;
4. Conference «Polish-Kazakh meetings - The relationship between chemistry and biology», **Poland**, 2023 y. 27 June;
5. XVI International Scientific and Practical Conference «Ecology. Radiation. Health» named after B.A. Atchabarov dedicated to the 70th anniversary of Semey Medical University, **Republic of Kazakhstan, Semey**, 2023 y. 28-29 August;
6. I International Forum of Young Scientists and students, **Republic of Kazakhstan, Shymkent**, 2023 y., December 6-8, **Diploma of the first degree**;
7. The 68th Annual General Assembly and Scientific Meeting of the Japan College of Rheumatology, **Japan, Kobe**, 2024 y. 18-20 April, **Travel Award Winner**;
8. Midterm Symposium APLAR-2024 (Mid-term Symposium APLAR-2024) and 7th Congress of Rheumatologists of Kazakhstan, **Kazakhstan, Almaty** 2024 y. 25-27 April.

The doctoral student won the **«TRAVEL SUPPORT GRANT»** from the organising Committee of the 68th Annual General Assembly and Scientific Meeting of the Japanese College of Rheumatology (JCR 2024) and was invited as a speaker **(Japan, Kobe)**.

Publications

1. New-onset systemic vasculitis following SARS-CoV-2 infection and vaccination: the trigger, phenotype, and outcome («Clinical Rheumatology», Great Britain; Q3 according to the Journal Citation Reports (Clarivate Analytics);
2. SARS-COV-2 as a trigger of IgA vasculitis: a clinical case and literature review («Rheumatology International», Germany; Q2 according to the Journal Citation Reports (Clarivate Analytics); the first author);

3. Diagnostic delays in systemic vasculitis: The causes, implications and outcome («Rheumatology International», Germany; Q2 according to the Journal Citation Reports (Clarivate Analytics); the first author).
4. The impact of the COVID-19 pandemic on patients with systemic vasculitis: a single-centre retrospective study («Rheumatology International», Germany; Q2 according to the Journal Citation Reports (Clarivate Analytics); the first author, the corresponding author);
5. Clinical and anamnestic features of patients with systemic vasculitis: a single-centre retrospective study («Rheumatology International», Germany; Q2 according to the Journal Citation Reports (Clarivate Analytics); the first author, the corresponding author);
6. Physicians' perceptions about antineutrophil cytoplasmic antibody-associated vasculitis (AAV): an online survey report in the time of the COVID-19 pandemic» («Clinical Rheumatology», Great Britain; Q3 according to the Journal Citation Reports (Clarivate Analytics); the first author);
7. Systemic vasculitis in Kazakhstan: a complex research approach («Central Asian Journal of Medical Hypotheses and Ethics» (CAJMHE); Kazakhstan; The list of publications recommended by the Committee for Quality Assurance in the field of Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan for the publication of the main results of scientific activity; the first author, the corresponding author).

List of scientific papers in the materials of international conferences

1. The prevalence of systemic vasculitis in the Turkestan region. «Modern medicine and pharmaceuticals: new approaches and current research» (Uzbekistan, Samarkand)
2. Vasculitis caused by vaccination against COVID-19. «COVID-19 and other topical infections in Central Asia» (Kazakhstan, Shymkent)
3. Awareness of doctors about systemic vasculitis. Dedicated to the 70 th anniversary of the Semey Medical University named after B.A. Atchabarov. «Ecology. Radiation. Health» (Kazakhstan, Shymkent)
4. The frequency of joint damage in systemic vasculitis. «Medicine of tomorrow: the scientific heritage of academician M.A. Aliyev» (Kazakhstan, Almaty)
5. Gastrointestinal involvement in systemic vasculitis: a retrospective study. International Conference 9th Polish-Kazakh Meeting: Relationship Between Chemistry and Biology (Poland)
6. Clinical and anamnestic features of patients with systemic vasculitis. «Prospects for the development of biology, medicine and pharmacy» (Shymkent, Kazakhstan)
7. Systemic vasculitis and organ damage: a single-centre Retrospective Study. «Mid-term Symposium APLAR-2024 and 7 th Congress of Rheumatologists of Kazakhstan» (Kazakhstan, Almaty)
8. The organ and system damage in systemic vasculitis: a single-centre retrospective study. «The 68th Annual Scientific Meeting of the Japan College of Rheumatology» (Japan, Kobe)

Intellectual property (patents, copyrights, inventions, etc.)

1. Recommendations for treating systemic vasculitis during COVID-19 and after vaccination against COVID-19. Certificate of entry of information into the State Register of Rights to Copyrighted objects (copyright certificate) №39155 dated September 21, 2023
2. Questionnaire to assess doctors' understanding of managing vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) (AAV) in COVID-19. Certificate of entry of information into the State Register of Rights to Copyrighted Objects (copyright certificate) №38061 dated July 21, 2023

The scope and structure

The study results are presented as a series of articles (7 publications). The volume of literature by the published articles totals 329 sources.