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RHEUMATOLOGY QUARTERLY

RQ
Rheumatology Quarterly

galenos yayınevi

March
2023

AIMS AND SCOPE

The Rheumatology Quarterly is a peer-reviewed periodical journal that publishes quarterly (March, June, September, December) in English electronically. The journal publishes original contributions in the form of experimental and clinical research articles, case reports and litrerature review, reviews, news, letters to the editor and authors, as well as announcements related to all topics of rheumatology.

The Rheumatology Quarterly aims to constitute a current scientific discussion platform and archive in rheumatology with the contribution of the disciplines related to rheumatology together. The journal intends to share its experiences with the international scientific community in a prestigious way and provide an academic contribution to the development of rheumatology science.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Title: The Rheumatology Quarterly

Journal abbreviation: Rheumatol Q

E-ISSN: 2980-1559

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Peer Review Process

The Rheumatology Quarterly uses an independent, unbiased, double-blind peer review process. Manuscripts are received and reviewed by the editor-in-chief, who directs them to the appropriate section editor. The section editor sends the manuscript to three independent referees. Referees are selected by the editorial board from among national and international experts in the area relevant to the study. The referees accept or reject the invitation to review the manuscript within two weeks. If they accept, they are expected to return their decision within 21 days. The associate editor reviews the referees' decisions, adds their own feedback, and returns the manuscript to the editor-in-chief, who makes the final decision. In case of disagreement among referees, the editor can assign a new referee.

The editor-in-chief, associate editors, biostatistics consultant, and English language editor may make minor changes to accepted manuscripts before publication, provided they do not fundamentally change the text.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

All submissions must be accompanied by a signed statement of scientific contributions and responsibilities of all authors and a statement declaring the absence of conflict of interests. Any institution, organization, pharmaceutical or medical company providing any financial or material support, in whole or in part, must be disclosed in a footnote (ICMJE Disclosure Form for Potential Conflict of Interest(s)).

The manuscript format must comply with the ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2018).

The presentation of the article types must be designed in accordance with trial reporting guidelines:

Human research: Helsinki Declaration as revised in 2013

Systematic reviews and meta-analyses: PRISMA guidelines

Case reports and litrerature review: The CARE case report guidelines

Clinical trials: CONSORT

Animal studies: ARRIVE and Guide for the Care and Use of Laboratory Animals

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GENERAL RULES

SUBMISSION REQUIREMENTS

- Cover Letter,
- "ICMJE Conflict of Interest Statement Form" (http://www.icmje.org/conflicts-of-interest/) for all contributing authors,
- A separate title page (Title Page should be submitted with all manuscripts and should include the title of the manuscript, name(s), affiliation(s), major degree(s) and ORCID ID of the author(s). The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be clearly listed. Grant information and other sources of support should also be included. Individuals who contributed to the preparation of the manuscript but did not fulfil the authorship criteria should also be acknowledged in the title page),
- Abstract divided into appropriate sections,
- Keywords (For indexing purposes, a list of 4–8 key words in English is essential),
- Article divided into appropriate sections,
- List of references styled according to "journal requirements",
- A blinded main text (Please exclude all information that may indicate an individual or institution from the main document to ensure a blinded review process),
- The Copyright Agreement and Acknowledgement of Authorship form (Please submit a wet-signed and scanned copy of the Copyright Transfer Form with your submission),
- Upload your title page and forms in the system to Potential Conflict of Interest category to ensure a blinded review process,
- Figures (Figures should be submitted as standalone images through the submission system in .JPG or .TIFF format),
- Ethics Committee Approval Statement (with decision/file no, date and name of the institution, for original articles).

Abstract

The research articles should consist of Objectives, Methods, Results and Conclusion sections and should not exceed 250 words. At least 3, a maximum of 6 keywords should be determined on the Abstract page, and the title of the article should be added.

Main Text

The introduction should consist of the Patients / Materials and Methods, Results, Discussion and References sections. Abbreviations should be standard and should be explained in parentheses when they are used first. Internationally accepted units should be used in the measurements.

Tables, Figures and Images

It should be numbered in the order of use in the text, and unnecessary use should be avoided. In the photographs used in the cases, permission should be obtained, and necessary measures should be applied to prevent recognition. Attention should be paid to the quality of photographs and drawings, if any. Editorial Board may request correction or renewal in tables, figures and pictures on the grounds that it is not of sufficient quality. Figures and pictures must be original. For the pictures, figures and graphics used in another publication to be published in our journal, the necessary permissions must be obtained by the authors and before applying for an article. A copy of the document indicating that the permit has been obtained must be sent to the journal with the article.

References

References should be selected from the ones that are up to date and necessary for the article. References in the text should be indicated in parentheses and numbered

according to the order of use. The name of the journals should be abbreviated in accordance with PubMed rules, and abbreviations should not be used in the names of journals which are not included here. Citation of proceedings should be avoided. Manuscripts accepted by a journal but not yet published can be documented as required and used as a source. Information other than this, including unaccepted articles, can be used by stating "unpublished observation" in the article. References should be written according to the examples below, and all the authors should be presented in references up to 6 authors, references which have more authors should be arranged in a way that "et al." abbreviation will be placed at the end of the first three authors. The responsibility for the accuracy of the references belongs to the authors.

Examples:

Periodical publication example:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow-acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Example of periodical publication published in an online journal:

Yurdakul S. Is there a higher risk of infection with anti-TNF-alpha agents, or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Example of book section:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include;

• The full title of the manuscript as well as a short title (running head) of no more than 50 characters,

• Name(s), affiliations and major degree(s) of the author(s)

• Grant information and detailed information on the other sources of support,

• The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author,

• Acknowledgement of the individuals who contributed to the preparation of the manuscript but do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for letters to the editor. The abstract of Original Articles should be structured with subheadings (Aim, Materials and Method, Results and Conclusion).

Keywords: Each submission must be accompanied by a minimum of three and a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations.

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Materials and Methods (with subheadings), Results, Discussion, Study Limitations, Conclusion subheadings.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with the international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and statistical software that was used the process must certainly be specified. Data must be expressed as mean±standard deviation when parametric tests are used to compare continuous variables. Data

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must be expressed as median (minimum-maximum) and percentiles (25th and 75th percentiles) when non-parametric tests are used. In advanced and complicated statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supported by confidence intervals (CI) and p values.

Editorial Comments: Editorial comments aim at providing brief critical commentary by the reviewers having expertise or with high reputation on the topic of the research article published in the journal. Authors are selected and invited by the journal. Abstract, Keywords, Tables, Figures, Images and other media are not included.

Review Articles: Reviews which are prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into high volume of publication and higher citation potential are taken under review. The authors may be invited by the journal. Reviews should be describing, discussing and evaluating the current level of knowledge or topic used in the clinical practice and should guide future studies. Please check Table 1 for limitations for Review Articles.

Case reports and litrerature review: There is limited space for case reports and litrerature review in the journal and reports on rare cases or conditions that constitute challenges in the diagnosis and treatment, those offering new therapies or revealing knowledge not included in the books, and interesting and educative case reports and litrerature review are accepted for publication. The text should include Introduction, Case Report, Discussion, Conclusion subheadings. Please check Table 1 for limitations for case reports and litrerature review.

Letters to the Editor: This type of manuscripts can discuss important parts, overlooked aspects or lacking parts of a previously published article. Articles on the subjects within the scope of the journal that might attract the readers' attention, particularly educative cases can also be submitted in the form of "Letter to the Editor". Readers can also present their comments on the published manuscripts in the form of "Letter to the Editor". Abstract, Keywords, Tables, Figures, Images and other media are not included. The text should be unstructured. The manuscript that is being commented on must be properly cited within the manuscript.

Images: Authors can submit for consideration an illustration and photos that is interesting, instructive, and visually attractive, along with a few lines of explanatory text. Images can include no more than 200 words of text. No abstract, discussion or conclusion are required but please include a brief title.

Table 1: Limitations for each manuscript type.

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	200 (Structured)	50	6	7 or total of 15 images
Review Article	5000	200	50	6	10 or total of 20 images
Case reports and litrerature review	1500	200	10	No tables	10 or total of 20 images
Letter to the Editor	500	N/A	5	No tables	No media
Scientific letter	900	N/A	10	No tables	2 or total of 4 images
Clinical Imaging/Visual Diagnosis	400	N/A	5	No tables	3 or total of 6 images
History	900	N/A	10	No tables	3 or total of 6 images

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REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author, and their publication approval is requested within two days of their receipt of the proof.

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Out of respect to the reviewers, journal staff and the Editorial Board, authors are asked to submit a withdrawal request only if the reasons are compelling and unavoidable. Withdrawal requests should be submitted in written form, signed by all contributing authors of the manuscript. Reasons for withdrawal should be stated clearly. Each request will be subject to the Editorial Board's review and manuscripts will only be assumed withdrawn upon Editorial Board's approval. Cases of plagiarism, authorship disputes or fraudulent use of data will be handled in accordance with COPE guidelines.

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INSTRUCTIONS FOR REVIEWERS

Please structure your review using the following headings:

A brief summary of manuscript:

• What is the intent of the study?

• What conclusions do the authors reach?

• Do you believe this study has previously been published in whole or in part?

The Title

• Does the title adequately reflect the content of the manuscript?

Keywords

• Are the keywords appropriate?

The Abstract

• Is it structured?

• Does the Abstract adequately summarize the manuscript?

• Can the Abstract be understood without reading the manuscript?

• Does it specify outcome measures, and provide salient statistics?

• Do any discrepancies exist between the Abstract and the rest of the paper?

The Introduction

• Is the Introduction brief?

• Is the rationale for conducting the study explained based on a review of the medical literature?

• Is the purpose of the study clearly defined? Is there a well-described hypothesis?

Materials and Methods

• Is the design of the methods appropriate to allow the hypothesis to be tested?

• Could another investigator reproduce the study using the Methods as outlined?

• Is the sample or participant recruitment described in detail with the inclusion and exclusion criteria?

• Have the authors obtained Informed Consent and Ethical Committee Approval (if relevant)?

• Do the authors specify the data acquisition and evaluation (e.g., the index test, the reference standard)?

• Are the statistical methods described? Are they appropriate?

Results

• Are the Results clearly explained?

• Is the order of presentation of the Results parallel the order of presentation of the Methods?

• Are the Results convincing and reasonable?

• Are there any Results given that are not preceded by an appropriate discussion in the Methods?

Discussion

• Is the Discussion concise?

• Does it begin with the most important finding and summarize key results?

• Does it relate exclusively to the results of the study?

• Does it compare the results with the relevant literature?

• Are the conclusions justified by the results found in the study?

• Are the unexpected results explained sufficiently?

• Is the clinical applicability of the study findings discussed?

• Are the limitations of the study clearly stated?

Figures and Graphs

• Are all figures referred to in the text?

• Are the figures and graphs correct and appropriately labeled?

• Is the number of Figures within the limitations of the Journal?

(Please check out Table 1 on the Instructions to Authors page)

• Do the figures and graphs adequately show the important results?

INSTRUCTIONS FOR REVIEWERS

• Do arrows need to be added to depict important or subtle findings?

• Are the figure legends self-sufficient and understood without making reference to the remainder of the manuscript?

Tables

• Do the tables appropriately describe the Results?

• Are the abbreviations used in the tables explained at the bottom?

References

• Does the reference list follow the style for the Journal?

• Is the number of references within the limitations of the Journal? (Please check out Table 1 on the Instructions to Authors page)

• Does the reference list contain obvious mistakes?

• Do any important references need to be added?

Final appraisal and decision

• Please summarize the Major strengths and Major weaknesses of the manuscript, and make your decision according to your answer to the following questions;

1. Does the article provide novel information (data, techniques, or idea) that is not already available in the literature?

If **yes,** please describe what you believe is new.

If **no,** ask the authors to explain what they consider new in their work. Otherwise, unless the paper has something else extremely important to present, the manuscript should likely be rejected.

2. Do the authors provide a solid rationale for conducting this study? If no, then the manuscript should likely be rejected.

3. Has the data analysis been performed appropriately?

If no, then the manuscript should likely be rejected, or major revisions should be requested.

4. Have the results been clearly and accurately presented? If no, then a major revision should likely be requested.

5. If the article is scientifically acceptable, but the text is poorly written, then a minor revision should likely be requested.

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ORIGINAL ARTICLES

CASE REPORT AND LITERATURE REVIEW

IMAGE ARTICLE

BIOTECHNOLOGY BY AMGEN®

AT THE FOREFRONT OF MODERN BIOTECHNOLOGY

FOUR DECADES OF EXPERIENCE IN BIOLOGICS[1]

- A 'biology-first' approach to drug discovery[2]

NEXT-GENERATION BIOMANUFACTURING FACILITIES[2]

- Expanding access to biologic treatment options with a pipeline of branded biosimilars[2]

Amgen has a presence in approximately 100 countries and regions worldwide, focussing on six therapeutic areas: cardiovascular disease, oncology, bone health, neuroscience, nephrology and inflammation.[1] Amgen has multiple biosimilar products in development in therapeutic areas that include oncology and inflammation.[2]

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Reference: 1. AMGEN Fact Sheet. C2020. Accessed 25/3/2020. Available from https://www.amgen.com/about/quick-facts/ **2.** AMGEN Our Strategy. C2017. Accessed 6/4/2020. Available from https://www.theamgendifference.com/our-strategy.html

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5 The treatment that physicians have trusted for 5 years[1]

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In axSpA patients;

- ✓ **FAST AND LASTING relief at every step[1-3*]**
- ✓ **Favorable and consistent SAFETY profile over 5 years[4-7]**
- ✓ **Lasting REMISSION over 5 years[7]**
- ✓ **TREATMENT EXPERIENCE in more than 875,000 patients[8,†]**

*Efficacy was shown in disease symptoms that are important for patients with AS or nr-axSpA with VERXANT.
†All around the world and in 7 indications (adult and pediatric). VERXANT is indicated in treatment of adult patients with axial spondyloarthritis, psoriatic psoriasis and plaque psoriasis.
AS=Ankylosing spondylitis; nr-axSpA=Axial spondyloarthritis without radiographic evidence.

References:
1. Verxant® (secukinumab) Summary of Product Characteristics **2.** Marzo-Ortega H, et al. Lancet Rheumatol. 2020;2: e339-46. **3.** Deodhar A et al. Arthritis Rheumatol. 2021;73(1):110-120. **4.** Baraliakos X, et al. RMD Open. 2019;5(2):e001005. **5.** Deodhar A, et al. Arthritis Res Ther. 2019;21(1):111. **6.** Schreiber S, et al. Ann Rheum Dis. 2019;78(4):473-479. **7.** Marzo-Ortega H, et al. The Lancet Rheumatology. 2020 June;2(6):e339-e346. **8.** Novartis data on file. Aralık 2021.

▼ This medicinal product is subject to additional monitoring. This triangle will ensure that new safety information is quickly identified. Reporting ensures continuous follow-up of risk-benefit ratio of this medicine. Healthcare professionals are expected to report the suspected adverse reactions to Turkish Pharmacovigilance Center (TUFAM www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0312 218 30 00, 0800 314 00 08; fax: 0312 218 35 99) and/or related pharmaceutical company officials.

Verxant® (Secukinumab) Basic Succinct Statement (BSS) Important note: Before prescribing, consult full prescribing information. Presentation: Lyophilised powder for solution for subcutaneous injection in a vial containing 150 mg of secukinumab. Indications: Plaque psoriasis: Verxant is indicated for the treatment of moderate to severe plaque psoriasis in adults who fail to respond to, or who have a contraindication to, or are intolerant to conventional systemic therapies including ciclosporin, methotrexate and PUVA. Psoriatic arthritis: Verxant, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease modifying anti rheumatic drug therapy has been inadequate. Ankylosing spondylitis: Verxant is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. Axial spondyloarthritis without radiographic evidence (nr-axSpA): VERXANT is indicated for the treatment of adult patients with axial spondyloarthritis who respond inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), have high C-reactive protein (CRP) levels and/or objective signs of inflammation evidenced by magnetic resonance imaging (MRI) without active radiographic evidence. Dosage and administration: Plaque psoriasis: The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg. For some patients, a dose of 150 mg may be acceptable. Psoriatic arthritis: For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg. For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg. Ankylosing spondylitis: The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. In patients with inadequate response (in patients with ongoing active ankylosing spondylitis), the dose can be increased to 300 mg. Each 300 mg dose is given as two subcutaneous injections of 150 mg. Axial spondyloarthritis without radiographic evidence (nr-axSpA): The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Contraindications: Verxant is contraindicated in patients who have/had severe hypersensitivity reactions to the active substance or to any of the excipients and in patients who have clinically important, active infection (e.g. active tuberculosis). Warnings and precautions: Infections: Caution should be exercised when considering the use of Verxant in patients with a chronic infection or a history of recurrent infection. If a patient develops a serious infection, the patient should be closely monitored and Verxant should not be administered until the infection resolves. Anti-tuberculosis therapy should be considered prior to initiation of Verxant in patients with latent tuberculosis. Verxant should not be given to patients with active tuberculosis. Inflammatory bowel disease: Caution should be exercised when prescribing Verxant to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis. Patients should be closely monitored. Hypersensitivity reactions: Rare cases of anaphylactic reactions have been observed during clinical trials. Administration of Verxant should be discontinued immediately and appropriate therapy initiated if an anaphylactic or other serious allergic reaction occurs. Vaccinations: Verxant should not be given concurrently with live vaccines. Pregnancy: Category C Breast-feeding: Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Verxant must be made taking into account the benefit of breast-feeding to the child and the benefit of Verxant therapy to the woman. Adverse drug reactions: Very common (≥1/10): Upper respiratory tract infections. Common (≥1/100 to <1/10): Oral herpes, rhinorrhea, diarrhoea. Uncommon (≥1/1,000 to <1/100): Oral candidiasis, tinea pedis, otitis externa, neutropenia, conjunctivitis, urticaria. Rare: Anaphylactic reactions Interactions: Live vaccines should not be given concurrently with Verxant. Overdose: In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately. Contents of container: Verxant is supplied in a colourless glass vial with a grey coated rubber stopper and aluminium cap with a white flip-off component containing 150 mg of secukinumab. Storage: Store in a refrigerator (2°C - 8°C). Shelf Life: 3 years. After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Marketing Authorization Holder: Farmanova Sağlık Hizmetleri Limited Şirketi Suryapı & Akel İş Merkezi, Rüzgarlıbahçe Mah. Şehit Sinan Eroğlu Cad. No: 6, 34805, Kavacık - Beykoz/İstanbul, Türkiye Manufactured by: Novartis Pharma Stein AG, Schaffhauserstrasse, CH-4332 Stein, Switzerland. This summary of product characteristics is prepared from Verxant (Secukinumab) full prescribing information approved on 15.11.2021 in Turkey.

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ACR20 = American College of Rheumatology 20% improvement criteria; cDMARD = conventional disease-modifying antirheumatic drug; DAS28-hsCRP = Disease Activity Score for 28 joints with high sensitivity C-reactive protein; IR = inadequate responder; JAK = janus kinase; LTE = long-term extension; MTX = methotrexate; RA = rheumatoid arthritis; SDAI = Simplified Disease Activity Index.

References: 1. Taylor PC et al. N Engl J Med 2017;376:652–62 (including supplementary appendix). **2.** UNAMITY®, SmPC 2022. **3.** Smolen JS et al. Rheumatology (Oxford) 2021;60:2256–66. **4.** Taylor PC et al. Ann Rheum Dis 2021 Oct 27;annrheumdis-2021-221276. doi: 10.1136/annrheumdis-2021-221276.

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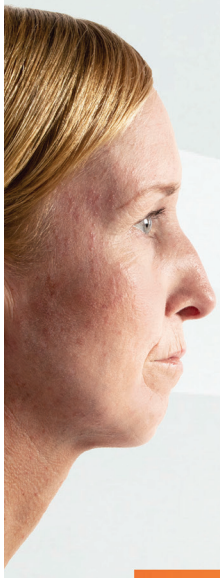
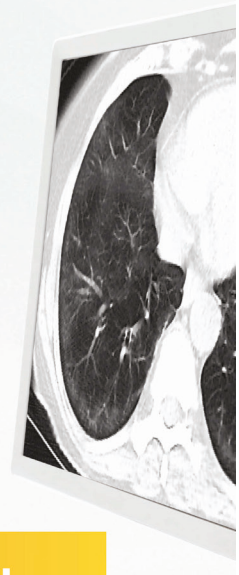


PULMONER FİBROZİS İLE MÜCADELE EDİN

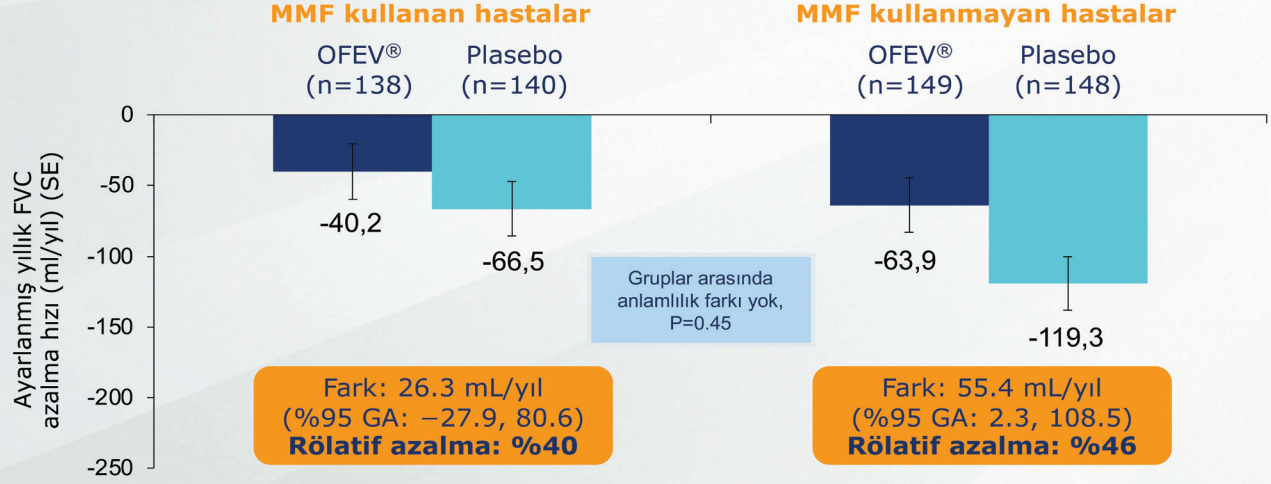
PROGRESYONU YAVAŞLATIN[1-4]



OFEV® ile akciğer fonksiyon kaybını yavaşlatarak İAH progresyonunu azaltın.[1-4]

İPF, progresif pulmoner fibrozis ve SSk-İAH'de tutarlı etkililik ve güvenlilik profili[1-4]

SSk-İAH hastalarında OFEV®, hem MMF ile birlikte hem de tek başına kullanıldığında FVC kaybını yavaşlatmıştır.[3]



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Referanslar: 1. OFEV® Kısa Ürün Bilgisi. **2.** Flaherty KR, et al. N Engl J Med. 2019;381(18):1718-1727.
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FORCED CHANGE IN RHEUMATOID ARTHRITIS TREATMENT DUE TO COVID-19 PANDEMIC: EFFECTS OF THE SWITCH FROM INTRAVENOUS TOCILIZUMAB TO SUBCUTANEOUS FORM

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Abstract

Aim: Rheumatoid arthritis (RA) is one of the most common chronic systemic autoimmune diseases that primarily affecting the synovial joints, causing progressive joint disability and involving extra-articular symptoms. The American College of Rheumatology (ACR) criteria published in 2010 were used for the diagnosis and classification of RA. The aim of RA treatment was to achieve remission or low disease activity. For this purpose, steroids, non-steroidal anti-inflammatory drugs, and conventional synthetic and biological disease-modifying antirheumatic drugs are used.

Material and Methods: Fifty-six patients with RA whose drug was switched from the intravenous (IV) tocilizumab form to the subcutaneous form in the Department of Internal Medicine Rheumatology-Immunology at Çukurova University Faculty of Medicine Research Hospital were included in the study. Patients with RA were diagnosed according to the criteria published by the 2010 ACR. The data were analyzed retrospectively.

Results: Forty-seven patients had initially received IV tocilizumab treatment. The baseline mean disease activity score (DAS-28) values were 7.65, and the mean treatment duration was 24.6 months. The mean DAS-28 values in the 3rd month of the patients who received IV tocilizumab treatment at baseline were 3.6. The decrease in DAS-28 from baseline was statistically significant ($p<0.0001$).

Conclusion: Consequently, subcutaneous tocilizumab therapy was effective and safe as IV therapy. The number of hospital admissions was less in the subcutan group, and Coronavirus disease-2019 (COVID-19) infection was less common. Subcutaneous therapy is a good alternative, especially during the pandemic period when patients can not easily access IV therapy and need to be isolated from the hospital.

Keywords: Rheumatoid arthritis, COVID-19 pandemic, tocilizumab, subcutaneous therapy

INTRODUCTION

Our aim in the study was to examine whether tocilizumab lost effectiveness in the transition to mandatory subcutaneous therapy in patients who received intravenous (IV) tocilizumab treatment during the Coronavirus disease-2019 (COVID-19) pandemic.

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases. It primarily affects the synovial joints and can cause progressive disability involves the joints, but should be

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considered a syndrome that includes extraarticular involvement, such as, pulmonary involvement, rheumatoid nodules, and vasculitis, and may be presenting with systemic comorbidities (1). The typical patient presents with swollen and tender small joints of recent onset, morning stiffness, and constitutional symptoms (fatigue and weakness). Abnormal laboratory tests may be found such as elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), serologically rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP). This symtomps are not specific for RA (2). New classification criteria for RA were presented in 2010 [American College of Rheumatology (ACR) criteria], providing inclusion of features of chronicity and poor prognosis (3,4).

The disease activity score (DAS-28) score was used to determine the disease activation in RA. The DAS-28 is a composite score derived from 4 of these measures (swollen joints, tender joints, ESR or CRP tests, global assesment of health). Ranges of DAS-28 scores that correspond to high, moderate, and low disease activity have been proposed. The high disease activity related to DAS-28 >5.1, moderate to DAS-28 of >3.2 to 5.1, and low disease activity is regarded in the range of 2.6 to 3.2. A cut-off point for "remission" has also been proposed (DAS-28 <2.6) (5).

Management strategies for patients with RA are directed toward the control of synovitis and the prevention of joint injury. The aim of treatment is to achieve and maintain remission or low disease activity by using disease-modifying antirheumatic drug (DMARD) therapy that is initiated early in the disease course (6).

Therapies used in RA are conventional synthetic and biological DMARDs. Non-biologic (traditional or conventional) DMARDs include methotrexate (MTX), hydroxychloroquine, sulfasalazine and leflunomide (7). Biologic DMARDs, which are produced by recombinant DNA technology and generally target cytokines or their receptors or are directed against other cell surface molecules. Such as the tumor necrosis factor-alpha inhibitors (infliximab, adalimumab etanercept , golimumab and certolizumab pegol) and the interleukin (IL)-6 receptor antagonists (tocilizumab and sarilumab). Other biologic response modifiers are the T-cell costimulation blocker (abatacept) and the anti-CD20 B-cell monoclonal antibody (rituximab). Targeted synthetic DMARDs, including several janus kina (JAK) inhibitors, are also available for use in RA. These include tofacitinib, baricitinib, and upadacitinib, which are orally administered small -molecule DMARDs that inhibit cytokines and signaling through interference with JAKs (8).

There are two IL-6 inhibitors, tocilizumab and sarilumab, available for using with MTX or as monotherapy, which have shown efficacy in biologic naive patients or patients resistant to other bDMARDs. Tocilizumab is a humanized immunoglobulin G1 anti-human IL-6 receptor antibody, competes for both the membrane-bound and the soluble forms of human IL-6 receptor, thereby inhibiting the binding of the native cytokine to its receptor and reducing the cytokine's effects (9). Tocilizumab had 8 mg/kg/month IV and 162 mg/week subcutaneous therapy for RA treatment. Recent research has found similar efficacy and safety data for both forms (10). IL-6 inhibition therapy is also used in giant cell arteritis, systemic juvenile idiopathic arthritis, and multicentric Castleman's disease treatments resistant to conventional therapies (11-13).

COVID-19 caused by a novel coronavirus, severe acute respiratory syndrome-coronavirus 2, has spread globally since December 2019, and the World Health Organization declared COVID-19 to be a pandemic on March 11, 2020 (14). The clinical manifestations of COVID-19 range quite dramatically from no symptoms whatsoever, to mild cough and pneumonia, to acute respiratory distress syndrome and death. Because cytokine release syndrome with elevation of IL-6 is considered to be associated with severe cases of COVID-19, IL-6 inhibitors such as tocilizumab are expected to be effective for its treatment (15). The republic of Turkey The Ministry of Health has issued guidelines for the management of COVID-19 infection treatment in November 2020. In this guideline, IL-6 inhibitor therapy is included for treating patients with COVID-19 associated macrophage activation syndrome (MAS) (16). Therefore, patients with RA patients experienced difficulties in obtaining the IV form of tocilizumab. Many patients were switched from IV tocilizumab treatment to the subcutaneous form. In this study, we examined the data of 56 patients with RA patients whose drug was switched from the iv form to the subcutaneous form.

MATERIAL AND METHODS

Fifty-six patients with RA whose drug was switched from the iv tocilizumab form to the subcutaneous form in the Department of Internal Medicine Rheumatology-Immunology at Çukurova University Faculty of Medicine Research Hospital were included in the study. Ethics committee approval was not obtained because our study was conducted by a retrospective file scanning method. Patients with RA were diagnosed according to the criteria published by the 2010 ACR. The data were analyzed retrospectively. DAS-28 ESR was used to score the disease activity. The demographic characteristics of the cases, the swollen joint counts, the tender joint counts (out of 28 joints), the patient and the doctor's global evaluation of disease activity, ESR, and CRP

levels from laboratory data were recorded. The clinical scores were evaluated using the visual analogue scale and the Health Assessment Questionnaire. It was assessed with the DAS-28 calculator (17). RF and anti-CCP test were determined using the ELISA test. RF level >20 IU/mL and anti-CCP level >15.6 U/mL were accepted as positive.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program version 20 software package (released 2011, IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA). Demographic variables were analyzed using descriptive analyses. Te normality of the distribution of continuous variables was checked using the Shapiro-Wilk test. Continuous parameters were compared using the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test. Results with p values less than 0.05 were regarded as statistically significant.

RESULTS

Fifty-six patients with RA who were followed up in our clinic were included in the study. Demographic and clinical data of the patients are given in Table 1. The mean age of 56 patients was 54.9 (21-70) years. Forty-nine were (87.5%) female and seven were (12.5%) male. Mean disease duration was 9.54 years. RF was negative in 15 (27%) patientsand positive in 41 (73%) patients. Anti-CCP was positive in 36 (64%) patients and negative in 20 (36%) patients. Nineteen patients (34%) were receiving tocilizumab therapy and DMARD therapy. Twenty patients (36%) were receiving concurrent steroid therapy. Before the treatment, the mean CRP and ESR values of the patients were 39 mg/L and 57 mm/hour. Mean laboratory values at the pre-treatment are given in Table 2.

Table 1. Demographic and laboratory characteristics of patients with RA

Gender	
Female	49 (87.5%)
Male	7 (12.5%)
Age (mean)	54.9 (21-70)
Disease age (mean) (year)	9.54 (2-19 year)
Rhematoid factor	
Negative	15 (27%)
Positive	41 (73%)
Anti-CCP	
Negative	20 (36%)
Positive	36 (64%)
Steroid therapy (≥4 mg methylprednisolone)	
Yes	20 (36%)
No	36 (64%)
DMARD therapy	
Yes	19 (34%)
No	37 (66%)

Anti-CCP: Cyclic citrullinated peptides, DMARD: Disease-modifying antirheumatic drug, RA: Rheumatoid arthritis

Forty-seven patients had initially received iv tocilizumab treatment. The baseline mean DAS-28 values were 7.65, and the mean treatment duration was 24.6 months. The mean DAS-28 values in the 3rd month of the patients who received IV tocilizumab treatment at baseline were 3.6. The decrease in DAS-28 from baseline was statistically significant ($p<0.0001$). All 47 patients who received iv therapy were switched to subcutaneous therapy after an average of 24.6 months. Nine patients were given direct subcutaneous treatment at the beginning. In a total of 56 patients, the mean DAS-28 value at the beginning of subcutaneous treatment was 4.2 and the mean therapy duration was 4.2 months. The mean DAS-28 value at 3 months was 3.47 and it was statistically significant in terms of treatment response ($p<0.0001$) (Table 3).

When subcutaneous treatment was evaluated in patients with RA; the DAS-28 value at the 3rd month was statistically significantly lower in patients on steroid therapy than patients who did not

Table 2. General laboratory characteristics

		Normal values
Beginning C-reactive protein (mg/L) (mean)	39 (±37.32)	0-9
Beginning eritrosit sedimantason rate (/hour) mean	57.43 (±22.68)	0-15
WBC/µL (mean)	8427.14	4800-10800
Neu/µL (neutrophil) (mean)	5261.61	1900-8000
Lymphosit/µL (mean)	2217.18	900-5200
Hemoglobin/µL (mean)	12.13	12-18
Mean corpusculer volume/µL (mean)	81.27	80-99
Platelets/µL (mean)	341.84	130-400
Creatinine (mg/dL) (mean)	0.75	0.3-0.8
Aspartate aminotransferase (U/L) (mean)	18.96	7-30
Alanine aminotransferase (U/L) (mean)	17.68	7-30

WBC: White blood cell

take steroid therapy. (p<0.0001). The DAS-28 value at the 3rd month was statistically significantly lower in patients on DMARD therapy than those without DMARD therapy (p<0.0001) (Table 4).

No statistically significant relationship was found between RF or anti-CCP positivity and response to treatment (Table 5). Drug-related adverse events and treatment-related infection rates were similar between both groups (p=0.07).

DISCUSSION

All the patients included in the study had received csDMARD treatments after the diagnosis of RA. Six patients were switched to tocilizumab treatment due to unresponsiveness to csDMARD treatment (DAS-28>3.2) and 47 patients due to unresponsiveness to other bDMARD treatment (DAS-28>3.2).

Markedly elevated pro-inflammatory cytokines (including IL-1 and IL-6) are associated with mortality at COVID-19 infection, and blocking the hyperinflammation may prevent disease progression (18). A few agents that target the IL-6 pathway have been evaluated in randomized trials for the treatment of COVID-19 infections; these include the IL-6 receptor blockers tocilizumab and sarilumab (19). Republic of Turkey Ministry of Health has issued guidelines for the management of COVID-19 infection treatment in November 2020. In this guideline, IL-6 inhibitor therapy is included for treating patients with MAS (16). Therefore, patients with RA patients experienced difficulties in obtaining the IV form of tocilizumab. Many patients were switched from IV tocilizumab treatment to subcutaneous form. Tocilizumab had 8 mg/kg/month IV and 162 mg/week subcutaneous therapy for RA treatment. Recent research has found similar efficacy and safety data for both forms (10).

In our study, the efficacy of treatment was successfully maintained in patients who were switched from IV tocilizumab therapy to subcutaneous therapy. When the mean DAS-28 values (mean DAS-28: 4.21) in the transition from IV to subcutaneous therapy were compared with the DAS-28 (mean DAS-28: 3.47) values in the 3rd month of subcutaneous therapy, the treatment efficacy was maintained (p<0001). When evaluated in terms of the number of hospital admissions, the subcutaneous therapy group was significantly less than that in the IV therapy group. For this reason, patients isolated themselves more from the hospital during the pandemic period. We did not find any COVID-19 infection in the follow-up of these patients. There were no treatment-related adverse events in either group. No treatment-related infection required hospitalization or antibiotherapy. There was no problem in compliance with the treatment in patients who switched from IV to subcutaneous therapy.

Table 3. General disease activation data for IV and SC treatment recipients

	IV therapy at the pre-treatment	Subcutaneous treatment
Patient number (n=56)	47 (84%)	56 (100%)
Duration of treatment (mounth) (mean)	24.6	4.2
Beginning DAS-28 value (mean)	7.65	4.21
3rd month DAS-28 value (mean)	3.66	3.47
Pre-treatment DAS-28 value and 3rd month DAS-28 value (p-value)	p<0.0001	p<0.0001

DAS-28: Disease activity score, IV: Intravenous, SC: Subcutaneous

Table 4. DAS-28 values according to treatment methods

	Pre-treatment DAS-28 value	IV therapy (3rd month DAS-28 value)	SC therapy (3rd month DAS-28 value)
DMARD therapy			
Yes	4.86	2.16	3.40
No	7.54	3.54	3.50
P-value	<0.0001	<0.0001	0.771
Steroid therapy			
Yes	5.81	2.60	2.70
No	7.09	3.33	3.89
P-value	0.079	0.840	<0.0001

DMARD: Disease-modifying antirheumatic drug, IV: Intravenous, SC: Subcutaneous, DAS-28: Disease activity score

Table 5. Effects of autoantibody presence on DAS-28 values according to treatment methods

	Pre-treatment DAS-28	IV therapy (3rd month DAS-28)	SC therapy (3rd month DAS-28)
RF positive (n=41)	6.84	3.10	3.47
RF negative (n=15)	6.06	2.99	3.47
P-value	p=0.327	p=0.804	p=0.999
Anti-CCP positive (n=36)	6.95	3.13	3.46
Anti-CCP negative (n=20)	6.06	2.96	3.4
P-value	p=0.228	p=0.702	p=0.926

RF: Rheumatoid factor, Anti-CCP: Cyclic citrullinated peptides, DAS-28: Disease activity score, IV: Intravenous, SC: Subcutaneous

Study Limitations

The limitation of our study was due to the small number of patients. Larger randomized controlled trials are needed in this area.

CONCLUSION

Consequently, subcutaneous tocilizumab therapy was effective and safe as IV therapy. The number of hospital admissions was less in the subcutan group, and COVID-19 infection was less common. Subcutaneous therapy is a good alternative, especially during the pandemic period when patients can not easily access IV therapy and need to be isolated from the hospital.

The clinical manifestations of COVID-19 range quite dramatically from no symptoms whatsoever, to mild cough and pneumonia, to acute respiratory distress syndrome, and death. For this reason, patients isolated themselves more from the hospital during the pandemic period. We did not find any COVID-19 infection in the follow-up of these patients. No treatment-related infection required hospitalization or antibiotherapy.

Ethics

Ethics Committee Approval: Ethics committee approval is not required as it is a retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., M.A.A., D.A.T., S.Ö., Design: E.K., M.A.A., D.A.T., S.Ö., Data Collection or Processing: E.K., M.A.A., D.A.T., S.Ö., Analysis or Interpretation: E.K., M.A.A., D.A.T., S.Ö., Literature Search: E.K., M.A.A., D.A.T., S.Ö., Writing: E.K., M.A.A., D.A.T., S.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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ANCA ASSOCIATED VASCULITIS: CLINICAL COURSE AND OUTCOME OF 44 PATIENTS FROM A SINGLE CENTER IN TURKEY

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Abstract

Aim: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of disease characterized by necrotizing, granulomatous inflammation of small to medium-sized blood vessels. The classification of vasculitis is performed according to the International Chapel Hill Consensus Conference, which was held in 2012; a system that classifies the disease according to the vessel size. According to this classification, ANCA-AAV is classified as granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis polyangiitis (EGPA). Although AAV is a rare disease with an incidence of about 20 per million population per year in Europe and North America. There is a slightly male preponderance. The aim of our study aimed to reveal the clinical features of ANCA-AAVs and to compare the effects of related organ involvement on prognosis

Material and Methods: Forty-four patients who were followed up with the diagnosis of ANCA-AAV between 2006 and 2020 at the rheumatology-immunology unit were included in our study. The data were analyzed retrospectively.

Results: In this retrospective study, 44 patients were included who were followed up with the diagnosis of AAV. The patients had 38 (86%) GPA, 4 (9%) MPA, 2 (4.5%) EGPA diagnoses. Forty-two patients were positive for ANCA (35 cytoplasmic-ANCA and 7 perinuclear-ANCA). ANCA test of two patients were negative. Ten of the patients with GPA had limited and 28 of them had severe disease. Forty-two patients were followed up for an average of 36 (3-168 months) months. The initial mean Birmingham vasculitis activity score of the patients was calculated as 19 (±7.512). The number of patients in clinical remission was 31 (71%), and the mean time to remission was 6 months. During the follow-up, 21 patients' disease relapsed, 2 patients quit followed up, and 3 patients died.

Conclusion: The variety of clinical symptoms of this curable disease may result as a delay for diagnose and treatment. The disease had a heterogeneous clinical presentation. Therefore, it is appropriate to make a patient-based decisions for management. In this study, we demonstrated the clinical diversity and the efficacy of cyclophosphamide and rituximab during induction therapy.

Keywords: ANCA-associated vasculitis (AAV), granulamatozis polyangitiis, BVAS

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INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a disease characterized by autoantibodies against the antigenic components of the neutrophilic cytoplasm and characterized by necrotizingand granulomatous inflammation of small to medium blood vessels. The most widely used classification system for systemic vasculitis is the International Chapel Hill Consensus Conference, which was held in 2012 that evaluates the disease according to the vessel size. According to this classification, ANCA-AAV is classified into 4 clinical groups: Granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis polyangiitis (EGPA), and renal limited vasculitis. Antineutrophil cytoplasmic antibodies are specific for proteinase 3 (PR3) or myeloperoxidase (MPO) and can be found in most patients with AAV (1). PR3 ANCA is most frequent in GPA (frequency 75%) whereas rarely found in EGPA (frequency 5%). MPO ANCA positivity is more frequent in patients with MPA (70% frequency) than GPA patients (20%). EGPA has different pathogenetic mechanisms, genetic features, and clinical findings than other diseases in this group (2). In AAVs, 10% of patients may reveal negative ANCA test. These patients are presented with a similar clinical course and comparable treatment response compared with the ANCA-positive group; however, but ANCA-negative patients are more likely to have kidney-limited disease or less severe systemic disease (3). Although AAV disease is rare with an incidence of 20 per million population per year in Europe and North America, it is the most common form of primary systemic vasculitis. There was a slight male preponderance. The incidence increases with age and has a peak in the 60-70 years (4). Constitutional symptoms (fatigue, weight loss, fever, joint-muscle pain) are evident and may occur several months before other symptoms have started. Respiratory symptoms are more common in GPA, and ground-glass densities, cavitation, or nodular lesions can be seen on thorax tomography. Upper respiratory tract involvement may present as rhinitis, sinusitis, otitis media, or granulomatous inflammation leading to septal perforation and nasal collapse (5). Upper airway involvement is less common in MPA, and lung involvement in MPA typically presents with alveolar hemorrhage and pulmonary fibrosis (6). Hearing loss, episcleritis/uveitis, purpuric rash in the lower extremities secondary to leukocytoclastic vasculitis, and peripheral neuropathy (mononeuritis multiplex) may be seen, but the central nervous system involvement is rare. Deep venous thrombosis may occur during the active phase of vasculitis (7,8). Renal involvement is common in AAV and is the most important cause of mortality. Patients with glomerular filtration rates (GFRs) <50 mL/min have a 50% risk of death or end-stage renal disease in 5 years. Renal involvement can be seen as a rapidly progressing glomerulonephritis (GN) with decreased kidney function accompanied by nephrotic proteinuria, microscopic hematuria, and, hypertension. Typically, pauci-immune focal necrotizing crescentric GN is seen on kidney microscopic examination. Higher proteinuria levels are associated with a higher percentage of crescent (9).

Treatment: AAV therapy includes a 2-step approach. The first step, an induction phase (first 6-12 months) with the aim of rapidly suppressing the inflammatory process and minimizing tissue and organ damage. The second is the maintenance step, which continues for 24-48 months aiming for remission (10). Standard therapy for induction in severe AAV includes a combination of glucocorticoids with cyclophosphamide (CYC) or rituximab (RTX). For refractory patients whom presented with no improvement within 4 to 6 weeks or with worsening disease activity, it is recommended that the initial induction agent may be ex changed with an alternative agent. CYC and RTX may be switched to each other (11). The 2-year mortality before effective treatment regimens in AAV (mostly due to kidney and lung involvement) was about 93%. Survival was improved with the introduction of glucocorticoids in 1948 and CYC in the 1960s (12). During remission induction therapy, treatment may have to be interrupted because of serious complications such as opportunistic infections and bone marrow suppression. Although long-term therapy is expected to control the disease, more than 50% of patients develop relapse during or after maintenance therapy. The heterogeneity of disease recurrency and ANCA positivity are the main factors affecting the treatment success. Therefore, it is appropriate to make a patient-based decision in treatment selection (13).

The aim of our study aimed to reveal the clinical features of ANCA-associated vasculitides and to compare the effects of related organ involvement on prognosis. The induction and maintenance treatments of 44 patients with ANCA-related vasculitis followed in our clinic were consistent with the literature. Genitourinary involvement, which is one of the rare sites of involvement, was present in 3 of our patients, and we wanted to share this rare involvement. In our study, we found that the majority of recurrence were renal and lower respiratory tracts.

MATERIAL AND METHODS

Forty-four patients who were followed up with the diagnosis of ANCA-AAV between 2006 and 2020 at the Rheumatology-Immunology Unit at the Research Hospital of Çukurova

University were included in our study. GPA, microscopic polyarteritis nodosa (MPAN), and EGPA patients were diagnosed according to the criteria published by the 1990 American College of Rheumatology. The data were analyzed retrospectively. On 05/04/2019, the approval of the Ethics Committee numbered 87 was received from Çukurova University. Birmingham Vasculitis Injury Index Version-3 was used to score the disease activity (14). ANCA test was determined by the indirect immunofluorescence method and was reported as cytoplasmic-ANCA (c-ANCA) and perinuclear-ANCA (p-ANCA) by subgroup analysis using enzyme-linked immunosorbent assay test. Respiratory and other system evaluations were evaluated using radiography and computed tomography. Biopsies were performed from the involved organs: Such as; lung, renal, skin, nasal septum, palate, and brain; histopathology examination and immunofluorescence staining were performed.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program version 20 software package (released 2011, IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA). Demographic variables were analyzed using descriptive analyses. Te normality of the distribution of continuous variables was checked using the Shapiro-Wilk test. Continuous parameters were compared using the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test. Results with p values less than 0.05 were regarded as statistically significant.

RESULTS

Forty-four patients with ANCA-AAV who were followed up in our clinic were included in the study. The patients were diagnosed as: GPA in 38 (86%) patients, MPA in 4 (9%) patients and EGPA in 2 (4.5%) patients. Demographic and clinical data of the patients are given in Table 1. The mean age of 44 patients was 49 (± 12.3) years. Twenty patients were (45%) female and 24 were (55%) male. Forty-two (42) patients were followed up for an average of 36 (3-168) months. Two patients quit follow-up after the first dose of remission induction therapy. Three patients died during follow-up. Forty-two patients were positive for ANCA (35 c-ANCA, and seven p-ANCA). ANCA test of two patients was negative. Patients with a negative ANCA test were diagnosed with GPA after a transthoracic lung biopsy. Ten patients were diagnosed with limited GPA (non-renal limited lung involvement). Systemic involvement of the patients was as follows: Upper respiratory tract 25 (57%), lung involvement 36 (82%), renal involvement 31 (71%), skin 16 (36%), mononeuritis multiplex 16 (36%), articular 18 (41%), eyes 10 (23%), testis 2 (5%), prostate 1 (2.5%) (Table 2).

Table 1. Demographic and general characteristics of patients with ANCA-associated vasculitis

Sex n (%)	
Female	20 (45%)
Male	24 (55%)
Age (mean) (SD)	49 (±12.3)
BMİ (mean) (SD)	28 (±5.3)
Tobacco n (%)	13 (30%)
Diagnosis n (%)	
GPA	38 (86%)
MPA	4 (9%)
EGPA	2 (4.5%)
Disease age (mean) (mounth)	36 (37.11-65.44)
The number of histopathological samples n, (%)	33 (75%)
Nose	17 (39%)
Lung	5 (11%)
Renal	9 (21%)
Skin	1 (2%)
Brain	1 (2%)
Comorbidity n (%)	27 (61%)
Organ involvement	
Upper respiratory tract n (%)	25 (57%)
Lower respiratory tract n (%)	36 (82%)
Renal n (%)	31 (71%)
Skin n (%)	16 (36%)
Mononeuritis multiplex n (%)	16 (36%)
Articular n (%)	18 (41%)
Eye n (%)	10 (23%)
Testicular n (%)	2 (5%)
Prostate n (%)	1 (2.5%)
ANCA during diagnosis	
c-ANCA n (%)	35 (80%)
p-ANCA n (%)	7 (16%)
ANCA negative	2 (4%)
BVAS (mean, during diagnosis) (SD)	19 (±7.512)
Remission n (%)	31 (71%)
Remission time (mean)	6 (5.08-7.93)
Relapses	21 (47%)
Relapses time (mean)	10.5 (11.74-28.25)
Regions of relapses	
Renal n (%)	6 (14%)
Upper respiratory tract n (%)	2 (6%)
Lower respiratory tract n (%)	13 (30%)
Retinal artery trombosis n (%)	1 (2%)

ANCA: Antineutrophil cytoplasmic antibody, BMI: Body mass index, EGPA: Eosinophilic granulomatosis polyangiitis, GPA: Granulomatous polyangiitis, MPA: Microscopic polyangiitis, BVAS: Birmingham vasculitis activity score, c-ANCA: Cytoplasmic-ANCA, p-ANCA: Perinuclear-ANCA

Lung involvement patterns were as follows: 19 of 36 patients had nodular lesions, and 17 had cavitary lesions. Biopsy was taken from 34 organs: Nose 17 (50%), lung 6 (17%), renal 9 (26%), skin 1 (3%), and brain 1 (3%). The initial mean Birmingham vasculitis activity score (BVAS) score of the patients was calculated as 19 (±7.512). The number of patients in clinical remission was 31 (71%) and the mean time to remission was six months.

Remission Induction and Maintenance Therapies

Remission induction treatments of 38 GPA patients were: 25 (65%) patients CYC [500 mg/m^2/month, intravenous (IV)], 10 (26%) patients RTX (375 mg/m^2/week, 4 weeks), 1 (2%) patient mycophenolate mofetil (2 g/day) and 2 (5%) patients methotrexate (MTX) (15-25 mg/week/sc). Two EGPA patients received pulse methylprednisolone (250-500 mg/day three doses) and MTX (15 mg/week/sc) treatments. Four MPAN patients received pulse steroid and IV CYC treatment. Plasmapheresis was applied ten times to 10 patients and for several indications. IV immunglobulin (0.4 gr/kg/day) treatment was given to 4 patients. Pulse methylprednisolone (250 mg-1000 mg/day/IV route) was given to 33 patients (Table 2). No statistically significant difference was observed between CYC and RTX treatments when evaluated for remission (p=0.409). There was no significant difference in the duration of remission between patients who were given CYC treatment and those who received RTX (p=0.281). Remission periods were similar in patients who received pulse steroids and who did not receive pulse steroid (p=0.801). There was a moderate positive correlation between baseline BVAS and remission periods (r=0.37, p=0.02). The number of patients who were given mycophenolate mofetil, MTX, and azathioprine (AZT) treatment was not eligible for statistical evaluation.

Thirty-nine patients received remission maintenance therapy: 15 (38%) patients AZT, 6 (15%) patinet MTX, 6 (15%) patients mycophenolate mofetil and 12 (30%) patients RTX.

Recurrence Data

Recurrence occurred in 21 (47.72%) patients during follow-up. The median time to relapse (median, 95% confidence interval) was 10.5 (11.7-28.2) months. Regions of recurrence were lung 13 (56%) renal 6 (26%) upper respiratory tract 2 (8%) retinal artery thrombosis 1 (4%). There was no statistically significant relationship between ANCA positivity and recurrence (p=0.267). No statistically significant relationship was found between tobacco use and relapse (p=0.380). There was no significant relationship between gender in recurrence frequency (p=0.567). There was no significant difference in patients who were given CYC or RTX treatments as remission induction therapy regarding recurrence and infection secondary to treatment (p=0.141, p=0.26).

Renal Involvement

In 31 patients with renal involvement, the initial median creatinine value was 1.32 mg/dL (0.24-7.41), and the mean GFR value was 66.93 mL/min/1.73 m^2 (±37.89). Hematuria was present in 23 (74%) patients and >1-g proteinuria was present in 22 (71%) patients. Five patients (16%) had proteinuria at the nephrotic level. Patients with renal involvement were similar in terms of remission and recurrence with the patients without renal involvement. There was no significant difference in remission and recurrence in patients who received CYC or RTX treatment (p=0.315, p=0.115). End -stage renal disease developed in two patients during follow-up.

Table 2. Features of treatment modalities and treatment-related complications

Pulse metilprednisolon (n,%)	33 (75%)
Remission induction (n, %)	
Cyclophosphamide (n, %)	29 (65%)
Rituximab (n, %)	10 (22%)
Mycophenolate mofetil (n, %)	1 (2%)
Methotrexate	2 (4.5%)
Remission maintenance (n, %)	39 (88%)
Azathiopurine (n,%)	15 (38%)
Methotrexate (n,%)	6 (15%)
Rituximab (n,%)	12 (30%)
Mycophenolate mofetil (n,%)	6 (15%)
Plazmapheresis(n,%)	10 (23%)
Complications during treatment n (%)	33 (75%)
Steroid myopathy	3 (10%)
Steroid induced diabetes	6 (18%)
Osteoporosis	3 (10%)
Hypogammaglobulinemia	1 (3%)
Deep vein thrombosis	3 (10%)
Avascular necrosis	1 (3%)
Severe infection n (%)	16 (46%)
Bacterial pneumonia	8 (50%)
Fungal infection	3 (19%)
Herpes zoster	2 (12.5%)
Tuberculozis	2 (12.5%)
Skin infection	1 (6.25%)
Trimethoprim-sulfamethoxazole prophylaxis n (%)	24 (55%)

Treatment Complications and Mortality

Thirty-four complications related to medications have occurred. These were: Severe infection in 16 (46%) patients, steroid myopathy in 3 (10%) patients, secondary diabetes mellitus in 6 (18%) patients, osteoporosis 3 (10%) patients, skin infection in 1 (6.25%) patients, hypo-gammaglobulinemia in 1 (3%) patient, catheter-related deep vein thrombosis in 3 (10%) patients, steroid-related avascular necrosis in 1 (3%) patient. A total of 16 patients had treatment-related severe infections: Bacterial pneumonia in 8 (50%) patients, pulmonary fungal infection in 3 (19%) patients, herpes zoster in 2 (12.5%) patients, pulmonary tuberculosis in 2 (12.5%) patients, and skin infections in 1 (6%) patient. Malignancy developed in 2 patients during follow-up. These were lung adenocarcinoma and basal cell carcinoma of the skin. A total of 3 patients died: Two patients died due to sepsis secondary to opportunistic lung infection. The other was due to acute renal failure based on chronic renal disease.

DISCUSSION

ANCA-AAV is a heterogeneous group of diseases characterized by chronic, necrotizing, and granulomatous inflammation of small to medium blood vessels. GPA typically presents with upper respiratory tract, lung, and renal involvement. MPAN is characterized by rapidly progressive GN and alveolar capillaritis (1,2). EGPA is systemic necrotizing vasculitis characterized by migrating infiltrates in the lung accompanied by allergic asthma, nasal polyposis, and eosinophilia (3). AAV is a rare disease with about 20 per million population per year in Europe and North America. There is a slight male dominance. Although GPA is more common in Northern Europe and Australia, there are geographic differences (4). In our retrospective review, GPA had numerical superiority in patients with total ANCA-AAV. In the literature, PR3-ANCA is most commonly associated with GPA (75%), MPO-ANCA is more commonly associated with MPA (60%) and EGPA (50-60%) (2). Similar to the data in our study, there were 89% PR-3 ANCA positivity in GPA, MPO-ANCA positivity in all patients in MPAN, 50% p-ANCA positivity in 50% c-ANCA in EGPA. This 100% p-ANCA positivity in MPAN may be due to the low number of patients. Ear, nose and throat manifestations can occur in patients with either GPA or MPA. However, they were higher in patients with GPA (estimated frequency is 90 percent versus 35 percent in MPA). Parenchymal lung nodules and cavities are a well-recognized manifestations in AAV (6). In our study, upper and lower respiratory tract involvement was founded 57% and 82%, respectively. These data were similar to those in the literature. The comparison of ANCA-AAV patients with other citations is presented in Table 3.

Renal involvement is more common in GPA and MPA, than in EGPA. In previously reported studies, GN was present in only 18 percentage of patients at presentation. However, GN developed in 77-85% of patients, usually within the first two years of disease onset (15). In our study, 31 (71%) patients had renal involvement at the time of diagnosis. In AAVs, varying subnephrotic-nephrotic proteinuria rates, microscopic hematuria, and active urinary sediment can be seen at the beginning and during the disease (16). Hematuria was presented in 23 (74%) patients, and subnephrotic proteinuria was presented in 22 (71%). Five patients (16%) had proteinuria at the nephrotic level. Urogenital manifestation is a rare feature of GPA that is present in <1 % of reported cases (16). In our series, two patients had testicular involvement, and one patient had prostate abscess.

Ocular involvement was present in 10 GPA patients (23%) included in the study. These were 4 episcleritis, 5 uveitis, and one retinal artery thrombosis. Considering the literature data, patients with AAV may develop episcleritis/scleritis, conjunctivitis, corneal ulceration, optic neuropathy, uveitis, and retinal vasculitis (17).

Patients with AAV may develop clinical manifestations involving the peripheral and central nervous systems, including mononeuritis multiplex, sensorial neuropathy, cranial nerve abnormalities, central nervous system lesions and sensorineural hearing loss (18). In our series, 16 patients had peripheral nervous system involvement and one patient had involvement in the form of a solid mass in the left cerebral hemisphere. The two-stage treatment of AAV consists of remission induction followed by a more extended period of maintenance of remission as soon as the treatment goal is achieved. The standard regimen for induction therapy in AAV includes a combination of glucocorticoids with CYC or RTX. CYC can be used in oral or IV regimens. There are several advantages of IV CYC, including lower cumulative dose, reduced exposure, bladder protection, and increased compliance (19).

CYCLOPS and CORTAGE studies evaluated the reduction in CYC-associated toxicity in AAV using IV pulse regimens instead of daily oral therapy. Although the total IV CYC dose was lower, the remission rates of both formulations were found to be clinically comparable (19). We also prefer the IV form in our patients because of its lower cumulative dose. Thus, we rarely met complications such as hematological malignancy and bladder pathologies associated with cumulative dose. Information from RTX in ANCA-associated vasculitis and rituximab versus cyclophosphamide in ANCA-associated renal vasculitis randomized controlled trials in 2010 supported the consideration of RTX as an option for induction therapy in AAV. The success of RTX and CYC in the induction of remission was similar (19). A total of 29 patients

received IV CYC (500 mg/m^2), and ten patients were treated with RTX (375 mg/m^2). Once remission induction goals are reached (usually within 3-6 months), maintaining remission reduces disease recurrence risk.

Withdrawal of glucocorticoid therapy has been identified as a strong predictor of relapse; therefore, it is common practice to keep patients on low doses of prednisone (or equivalent) as part of the maintenance regimen. AZT, MTX, and mycophenolate mofetil have proven to be as effective as CYC for AAV maintenance therapy in randomized trials (Table 3) (20-28).

Study Limitations

First, the number of patients is not enough. In particular, the induction treatment distributions were not homogeneous, and treatment comparisons could not be clearly demonstrated.

CONCLUSION

Patients with GPA and MPA still have a higher mortality rate than the general population. Untreated patients have an approximately 90 percent mortality rate within two years.The long-term survival in patients with GPA and MPA has improved dramatically since the additions of CYC and RTX to the therapeutic regimen. Patients with GPA and MPA reported a 2.7-fold increased risk of death in patients than the general population. Pulmonary hemorrhage and end-stage renal disease (ESRD) are the most common causes of death in ANCA-AAV. In our study, 3 patients died. Looking at the causes of death, two patients died from sepsis secondary to opportunistic lung infection. The other died from acute renal failure developed on the basis of chronic renal failure. AAVs are a group of diseases with high mortality without treatment, so that diagnosis and treatment should not be delayed.

Table 3. General demographics of some ANCA-associated vasculitis studies. Comparison of clinical involvement sites

	Shobha et al. (23)	Kim and Song (24)	Holle et al. (25)	Kumar et al. (26)	Koldingsness and Nossent (27)	Reinhold-Keller et al. (28)	Present series (Turkey)
Number (n)	60	45	445	25	55	155	44
Age (mean)	44	51	51	33.5	50	48	49
M/F	1.4/1	1/1.3	1/1	1/1.7	1.6/1	1/1.04	1.2/1
Duration of analysis (years)	14	26	36	12	15	27	14
Clinical features (%)							
Upper respiratory	21	91	98	84	80	93	57
Lung	63	66	60	84	60	55	82
Renal	70	40	60	72	76	54	71
Articular	27	35	73	44	64	61	41
Ocular	11	40	40	64	38	40	23
Periferic nervous system	25	37	33	4	35	21	36
Skin	48	29	26	32	31	21	36
Testis	-	-	-	-	-	-	5
ANCA positivity	93	65	81	70	88	84	c-ANCA 80% p-ANCA 16%
BVAS-3 score	21.5 (17-44)	13.1 (4-22)	-	-	23 (4-46)	-	19 (7-42)
Mortality	18	22	10		0.2	14	6

M: Male, F: Female, ANCA: Antineutrophil cytoplasmic antibody, BVAS-3: Birmingham Vasculitis Injury Index Version-3, c-ANCA: Cytoplasmic-ANCA, p-ANCA: Perinuclear-ANCA

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Çukurova University Clinical Research Ethics Committee (no: 87, date: 05/04/2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Design: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Data Collection or Processing: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Analysis or Interpretation: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Literature Search: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Writing: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö.

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THE COURSE AND OUTCOMES OF COVID-19 IN PATIENTS WITH TAKAYASU ARTERITIS: CASE SERIES OF 15 PATIENTS FROM A TERTIARY SINGLE CENTER

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Abstract

Aim: Coronavirus disease-2019 (COVID-19) has affected more than three hundred million individuals, and many risk factors for increased mortality and morbidity in COVID-19 have been defined. There are many studies evaluating the course of COVID-19 in inflammatory rheumatic diseases, however, fewer data are available for patients with Takayasu arteritis (TAK). This study assessed the characteristics and outcomes of TAK patients with COVID-19.

Material and Methods: A phone survey was conducted among TAK patients that are followed up in our clinic between February 2021 and March 2021. All patients were asked whether they were diagnosed with COVID-19 during the pandemic. The patients who had a history of COVID-19 were asked about the symptoms, hospitalization status, and treatment received for COVID-19. Information about their chronic diseases was obtained from the patient files.

Results: Among 118 TAK patients, 15 had COVID-19 during the first year of the pandemic; 13 were female, and the mean age was 42.5±12.04 years. Nine of the patients were taking prednisone therapy, 12 were taking conventionally synthetic disease-modifying antirheumatic drugs (csDMARDs), 7 patients were taking biological disease-modifying antirheumatic drugs (bDMARDs), and 5 patients were taking a combination of csDMARD and bDMARD therapy when they were diagnosed with COVID-19. Two patients were hospitalized, and one of them was admitted to the intensive care unit for 5 days. All the patients fully recovered, and there was no mortality related to COVID-19.

Conclusion: Our data suggest that there is no increased risk for morbidity or mortality related to COVID-19 in TAK patients.

Keywords: Takayasu arteritis, COVID-19, SARS-CoV-2

INTRODUCTION

Patients with inflammatory rheumatic diseases (iRMD) receiving immunosuppressive therapy have an increased risk of severe infections (1,2). Since the start of the coronavirus disease-2019 (COVID-19) pandemic, a significant concern among rheumatologists has been raised.

Recent studies have evaluated the severity of COVID-19 in patients with iRMD, and it has been reported that glucocorticoid use is associated with severe disease (3-5). Also, the risk factors for severe COVID-19 in patients with iRMD were identified as risk factors in the general population, such as male gender, older age, hypertension, and obesity (6). Strangfeld et al. (7) reported

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that higher disease activity, higher dosages of glucocorticoids, and immunosuppressant use were associated with COVID-19 related death. Currently, there is no large study that is specifically evaluating the impact of COVID-19 among Takayasu arteritis (TAK) patients. In a case report, two TAK patients had a full recovery from COVID-19 and did not require hospitalization (8). In another published report, four TAK patients had confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, and 1 of them who had multiple comorbidities died (9). This study assesses the outcome of COVID-19 in patients with TAK.

MATERIAL AND METHODS

This case series includes patients with TAK and confirmed SARS-CoV-2 infection by a positive real-time polymerized chain reaction (RT-PCR) test from the nasopharyngeal swab between March 2020 and March 2021. A phone survey was conducted between February 2021 and March 2021 among TAK patients that are followed up at our clinic to ask whether they had confirmed SARS-CoV-2 infection during the pandemic.

Demographic characteristics, comorbidities, disease duration, disease status at the last visit, and patient medications were recorded from the patient files. The patients were asked about the time of the COVID-19 diagnosis, contact with a COVID-19 patient, symptoms, hospital admission status, immunosuppressive medication use during infection, and the treatment received for COVID-19.

The study protocol was approved by the Institutional Review Board (no: 09.2021.850) and carried out following the Declaration of Helsinki. All patients provided consent for the use of their clinical and demographic data.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp, Armonk, NY). Results were expressed as mean and standard deviation for parametric data, and frequency (%) for categorical data.

RESULTS

A total of 118 patients with TAK could be contacted by phone and included in the study. Among them, 15 patients with TAK had a SARS-CoV-2 infection confirmed by an RT-PCR test from the nasopharyngeal swab, and 2 of them also had suggestive thoracic computed tomography (CT) scans. All the patients had the infection before the COVID-19 vaccination. The mean age of the patients was 42.50±12.04 years, and 13 (86.6%) of them were female. The mean body mass index of the patients was 25.70±4.96 kg/m^2, and 3 of them were obese. Nine of the patients were taking prednisone therapy during infection, and 3 of them were using a dosage of ≥10 mg/day. Twelve patients were taking conventionally synthetic disease-modifying antirheumatic drugs (csDMARDs), seven were taking biological disease-modifying antirheumatic drugs (bDMARDs), and five were taking a combination of csDMARD and bDMARD therapy. Three of the patients taking bDMARDs were using tocilizumab, two were using adalimumab, and two were using infliximab therapy. One patient was in remission and was not using any immunosuppressive treatment for five years. During the last rheumatology visit 6 months before the diagnosis of COVID-19, 4 of the patients were accepted to have active disease, and 3 of them were taking moderate to high dose glucocorticoids during the infection period. The demographic and clinical characteristics of the patients are shown in Table 1.

All the patients stopped taking their immunosuppressive medications, except glucocorticoids, during COVID-19.

Close contact history with a COVID-19 patient was present in 7 patients. The most common symptom was fatigue, followed by cough and fever. Pneumonia was detected on thoracic CT scans in 2 patients, and both of them were hospitalized. The other patients had a non-severe disease, and a chest X-ray or thoracic CT scan was not performed.

COVID-19 treatment guidelines defined by the Ministry of Health of Turkey have recommend favipiravir as a first-line treatment agent to all patients with a confirmed COVID-19 diagnosis (10). Therefore, all 15 patients had used favipiravir treatment at a dosage of 1,600 mg twice daily on day 1, 600 mg twice daily on days 2-5.

Two of the 15 patients required hospital admission. One of them was taking infliximab 300 mg/6 weeks (the last infusion was 4 weeks ago), methotrexate 15 mg/week, and prednisone 5 mg/day for TAK when COVID-19 diagnosis was confirmed and hospitalized for 5 days and followed up with nasal oxygen and did not require admission to intensive care unit (ICU) or mechanical ventilation. The patient was given favipiravir, dexamethasone 6 mg/day, enoxaparin 4,000 IU/day, and one plasma exchange therapy during hospitalization.

The other patient who was taking leflunomide 20 mg/day and prednisone 7.5 mg/day for TAK was admitted to the hospital for a severe asthma attack and had a fever after the first week of hospitalization, and COVID-19 diagnosis was confirmed. She was hospitalized for 30 days and required ICU admission and non-invasive mechanical ventilation for 4 days because to comorbidities, including severe asthma and chronic thromboembolic pulmonary hypertension.

Table 1. Clinical features of Takayasu arteritis patients with confirmed COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Demographics								
Age (years)	65	46	21	31	49	38	50	46
Gender	Female	Female	Female	Female	Female	Female	Male	Female
Comorbidities	DM	HT	None	None	None	HT	None	CVD
Body mass index (kg/m^2)	23.62	34.85	21.37	29.76	31.23	28.13	23.63	26.67
Disease characteristics								
Disease duration (months)	96	8	48	72	60	36	14	130
Disease activity at last visit	Active	Inactive	Inactive	Active	Inactive	Inactive	Inactive	Inactive
Prednisone, mg/day	None	2.5	None	15	5	5	5	None
csDMARD	MTX 15 mg/week	MTX 15 mg/week	None	AZA 2x50 mg	MTX 15 mg/week	AZA 2x50 mg	AZA 3x50 mg	None
bDMARD	None	None	TOC 162 mg/week	ADA 40 mg/2 weeks	INF 300 mg/6 weeks	INF 400 mg/8 weeks	ADA 40 mg/2 weeks	None
COVID-19 infection								
Symptoms	Fatigue, headache	Fatigue	Fatigue, fever, cough	Fatigue, cough	Fatigue, fever, cough	Fatigue, cough	None	Fever, diarrhea
Contact with COVID-19 patient	None	Yes	Yes	None	None	Yes	Cough	Yes
Treatment for COVID-19	HCQ Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir Dexamethasone Enoxaparin Plasma exchange	Favipiravir	Favipiravir	Favipiravir
Hospital admission	None	None	None	None	Yes	None	No	None
Length of hospitalization (days)	-	-	-	-	5	-	-	-
Oxygen supplementation	-	-	-	-	Yes	-	-	-
ICU admission	-	-	-	-	None	-	-	-
Outcome	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

Table 1. Continue

	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
Demographics							
Age (years)	50	48	40	34	29	31	60
Gender	Female	Female	Female	Male	Female	Female	Female
Comorbidities	CVD	HT	None	None	None	None	CTEPH, CVD, HT
Body mass index (kg/m^2)	22.94	16.20	29.55	23.12	19.53	24.84	30.20
Disease characteristics							
Disease duration (months)	26	60	108	72	80	28	120
Disease activity at last visit	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Active
Prednisone, mg	None	2.5	5	15	None	None	7.5
csDMARD	MMF 2x500 mg	LEF 1x20 mg	LEF 1x20 mg	AZA 2x50 mg	None	MTX 10 mg/week	LEF 1x20 mg
bDMARD	None	None	None	TOC 162 mg/ week	TOC 162 mg/week	None	None
COVID-19 infection							
Symptoms	Fatigue, cough	Back pain, myalgia	None	Fatigue, fever, cough	Fatigue, cough	Fatigue, cough	Fever, cough
Contact with COVID-19 patient	None	Yes	Yes	Yes	None	None	None
Treatment for COVID-19	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir Dexamethasone Enoxaparin
Hospital admission	None	None	None	None	None	None	Yes
Length of hospitalization (days)	-	-	-	-		-	30
Oxygen supplementation	-	-	-	-	-	-	Yes
ICU admission	-	-	-	-	-	-	Yes
Outcome	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

ADA: Adalimumab, AZA: Azathioprine, bDMARD: biological disease-modifying antirheumatic drugs, csDMARD: conventional synthetic disease-modifying antirheumatic drugs, CTEPH: Chronic thromboembolic pulmonary hypertension, CVD: Cardiovascular disease, DM: Diabetes mellitus, HCQ: Hydroxychloroquine, HT: Hypertension, ICU: Intensive care unit, INF: Infliximab, LEF: Leflunomide, MMF: Mycophenolate mofetil, MTX: Methotrexate, TOC: Tocilizumab, COVID-19: Coronavirus disease-2019

A patient who had a mild COVID-19 disease had pulmonary thromboembolism 2 weeks after the infection, and his symptoms resolved after starting anticoagulation. No deaths were observed related to COVID-19 among TAK patients.

DISCUSSION

This study describes the largest cohort of COVID-19 cases in TAK patients. Among TAK patients that were followed up in our clinic, 15 of them had a confirmed diagnosis of SARS-CoV-2 infection. Of these 15 patients, all were using an immunosuppressive medication except one patient, and 7 of them were using bDMARDs. Two of the patients were hospitalized, and all of them had full recovery from the infection. Tomelleri et al. (8) reported 2 TAK patients with COVID-19 with no hospitalization or death. Comarmond et al. (9) reported 4 TAK patients with COVID-19, and only one of them with multiple comorbidities died, and the other 3 patients had a full recovery.

The effect of immunosuppression on the course of COVID-19 is unknown. In the first report of COVID-19 Global Rheumatology Alliance registry including 600 patients, bDMARD monotherapy was associated with a lower risk of hospitalization (11).

In the second report of COVID-19 Global Rheumatology Alliance registry, including 3,729 patients, treatment with bDMARDs, except for rituximab were not associated with a higher risk of death compared with methotrexate monotherapy. However, azathioprine and mycophenolate were related to a higher risk

of death than methotrexate monotherapy (7). Glucocorticoid exposure of ≥10 mg/day was associated with an increased risk of a worse prognosis of COVID-19 (7,11). In our cohort, only 2 patients were taking prednisone ≥10 mg/day, and both of them had mild COVID-19 disease. Also, despite the use of csDMARD and bDMARD therapies in TAK patients, there is no mortality related to COVID-19, but our sample size is limited to make a definitive comment on this issue.

Recent studies reported that the major risk factors for severe COVID-19 in patients with rheumatic diseases are comorbidities and older age (7,11), similar to the general population (12,13). In our cohort, the patient hospitalized for one month was 60 years old and had multiple comorbidities. Also, both the patients who were hospitalized had obesity. Despite the limited number of patients, this could be interpreted as the risk factors for severe COVID-19 in TAK patients are similar to the general population. Furthermore, 14 of the 15 patients were under 65 years of age, which can be a reasonable explanation for the lower severity of COVID-19 in this study.

In our cohort, 2 of the 15 TAK patients (13.3%) had required hospitalization due to COVID-19. In one of the largest studies from Turkey, which investigated the outcomes of COVID-19 in patients with iRMD, 30% of the patients had required hospitalization and oxygen support, 13% of the patients were treated in the ICU, and 10% of the patients had died (14). Also, our tertiary center was one of the biggest pandemic hospitals in Istanbul. During the second wave of pandemic between November 2020 and April 2021, the hospitalization rate among all PCR-positive patients admitted to the hospital was 22.4% (unpublished observation). In a study assessing COVID-19 infection among patients with Behçet's syndrome, no greater risk of severe infection was found compared with the general population (15). It seems like there is a lower hospitalization rate in TAK patients compared to the general population in our region, but there is a need for a more detailed comparison with age, sex, and comorbidity-matched cohorts.

Study Limitations

This study has several limitations. We had a limited number of patients to make definitive comments on the risk factors for severe COVID-19 in TAK patients. We could only contact 118 of the 201 TAK patients (58.7%) who followed up at our clinic; therefore, we might have missed some patients that had COVID-19 infection. Also, due to the retrospective study design, we could not assess the patients' disease activity during infection. However, this is the largest cohort to report the characteristics and outcomes of COVID-19 in TAK patients.

Despite the limited number of patients, our data suggest that there is no increased risk for mortality related to COVID-19 in patients with TAK. Further studies must fully understand the clinical characteristics and prognosis of COVID-19 in TAK patients.

CONCLUSION

Our data suggest that there is no increased risk for morbidity or mortality related to COVID-19 in TAK patients. Further studies with a larger sample size are needed to confirm these results.

NOTE: The study was accepted as a poster in the EULAR 2022 congress and the abstract was published with the DOI number "10.1136/annrheumdis-2022-eular.4528".

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Marmara University Clinical Research Ethics Committee (no: 09.2021.850, date no: 02.07.2021).

Informed Consent: All patients provided consent for the use of their clinical and demographic data.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.S., S.K.A., K.Y.A., A.A., H.D., F.A.Ö., Concept: G.S., H.D., F.A.Ö., Design: G.S., H.D., F.A.Ö., Data Collection or Processing: G.S., S.K.A., K.Y.A., A.A., H.D., F.A.Ö., Analysis or Interpretation: G.S., H.D., F.A.Ö., Literature Search: G.S., S.K.A., K.Y.A., A.A., Writing: G.S., H.D., F.A.Ö.

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RAPID3 SCORE CAN PREDICT DISEASE ACTIVITY IN PRIMARY SJÖGREN'S SYNDROME

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Abstract

Aim: Sjögren's syndrome (SS) is a chronic autoimmune disease that causes salivary and lacrimal gland dysfunction, resulting in oral and ocular dryness. The European League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI) is a systemic disease activity index measuring disease activity in patients with SS. The ESSDAI includes 12 domains. The EULAR SS Patient-Reported Index (ESSPRI) is used to evaluate dryness, fatigue, and pain symptoms, and their impact on the disease. Routine Assessment of Patient Index Data 3 (RAPID3) is used to evaluate disease activity in patients with rheumatoid arthritis, which is another inflammatory disorder. This study evaluates whether RAPID3 is useful in primary SS.

Material and Methods: In this cross-sectional study, 30 patients with primary SS were enrolled. ESSDAI, ESSPRI and RAPID3 scores were recorded. Chi-square, Mann-Whitney U test and Pearson correlation analysis was performed for the statistical analysis.

Results: Mean ESSDAI, ESSPRI, and RAPID3 scores were 3.8±3.6, 5.8±1.7, and 14.8±5.2, respectively. ESSPRI and RAPID3 scores were positively correlated ($r=0.669$, $p<0.001$). Additionally, when we set the cut-off value to 12 on the RAPID3 score (>12 accepted as active, and ≤12 accepted as inactive), ESSPRI score was significantly higher in active patients (6.4±1.4 vs 4.1±1.4, $p=0.002$). However, there was no relationship between the RAPID3 and ESSDAI scores.

Conclusion: In SS, it is difficult to detect disease activity. Comorbid psychosomatic diseases affect the set detecting global disease activity. These results suggest that RAPID3 may be useful to detecting disease activity in primary SS.

Keywords: Sjögren's syndrome, disease activity, Routine Assessment of Patient Index Data 3

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease of unknown origin that causes salivary and lacrimal gland dysfunction (1). SS has a wide variety of presentations, ranging from the local involvement of exocrine glands with keratoconjunctivitis sicca and xerostomia to the systemicand extraglandular involvement of multiple organs (2). Reported symptoms such as fatigue, arthralgia and chronic process have been associated with reduced health-related quality of life. Activity indices were used to assess disease severity, progression,

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and evolution. They can help prevent or delay damage by identifying patients with active disease that could be altered by treatment and selecting subgroups with more severe disease (3). A therapeutic approach to SS compared to other autoimmune diseases is also unclear because there is little consensus on which treatment to use and when for systemic involvement (4). Treatment is decided on an individual basis according to disease activity and the presence and extent of extraglandular manifestations (5). We are trying to determine the treatment response with activity indices. Therefore, good activity indices are required in SS and other connective tissue diseases. The European League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI) is a systemic disease activity index measuring disease activity in patients with SS (6). The ESSDAI includes 12 domains. The EULAR SS Patient-Reported Index (ESSPRI) is used to evaluate dryness, fatigue, and pain symptoms, and their impact on the disease (7). Routine Assessment of Patient Index Data 3 (RAPID3) is used to evaluate disease activity in patients with rheumatoid arthritis, which is another inflammatory disorder (8).

One patient-only index, termed the RAPID3, can be scored in fewer than 10 s on a Multidimensional Health Assessment Questionnaire (MDHAQ), compared to about 42 s for a standard HAQ, and 90 s for a quantitative 28-joint count (9-11). We think that it is an index that can be used in SS as well since it provides faster and shorter results. This study evaluates whether RAPID3 is useful in primary SS.

MATERIAL AND METHODS

Thirty patients with primary SS were enrolled in this cross-sectional study. ESSDAI, ESSPRI, and RAPID3 scores were recorded. SS patients were recruited from patients who applied to the rheumatology outpatient clinic, met the diagnostic/classification criteria, and agreed to participate in the study. Those under the age of 18 and over the age of 65, pregnant women, those in the lactation period, those with active infection, poorly controlled diabetes, or heart failure, and those with malignancy were excluded from the study. The results of routine tests (fasting blood sugar, creatinine, alanine aminotransferase, blood count, sedimentation and C-reactive protein, anti-nuclear antibody, anti-Ro, anti-La) of the patients were recorded. All the cases included in the study were first informed about their diseases. Afterwards, the purpose of the study was explained verbally and in writing, and an informed consent form was signed by the participants who agreed to participate in the study. Our study was found to be ethically appropriate and approved by the Ethics Committee of Fırat University (decision no: 01, date no: 24.02.2015).

Statistical Analysis

Statistical analyses were conducted using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Chi-square, Mann-Whitney U test, and Pearson correlation analysis were performed for the statistical analysis. A p value <0.05 is accepted as statistically significant.

RESULTS

Demographic and clinical data of the patients are given in Table 1. Mean ESSDAI, ESSPRI, and RAPID3 scores were 3.8±3.6, 5.8±1.7, and 14.8±5.2, respectively. ESSPRI and RAPID3 scores were positively correlated ($r=0.669$, $p<0.001$) (Table 2). Additionally, when we set the cut-off value to 12 on the RAPID3 score (>12 accepted as active, and ≤12 accepted as inactive), ESSPRI score was significantly higher in active patients (6.4±1.4 vs 4.1±1.4, $p=0.002$). However, there was no relationship between the RAPID3 and ESSDAI scores (Table 2). The schirmer test was positively correlated with tear break-up time (BUT) ($r=0.573$,

Table 1. Demographics and clinical variables

	SS (n=30)
Mean ageand years	51.0±8.7
Disease duration, years	6.3±4.6
Sex, % females	100
WBC, 10^3/µL	5.9±1.8
Hemoglobin, g/dL	13.3±1.5
ESR, mm/h	19.5±16.4
CRP, mg/dL	7.2±13.5
ANA positivity, %	83.3
Anti-Ro positivity, %	65.5
Anti-La positivity, %	46.2
HAQ	32.4±4.9
Schirmer test, mm	11.4±6.4
BUT, sec	3.2±1.8
Lissamine green score	2.2±1.1

SS: Sjögren's syndrome, WBC: White blood cell count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: Anti-nuclear antibody, HAQ: Health assessment questionnaire, BUT: Break-up time

Table 2. The correlation between the activity indices

		ESSPRI	ESSDAI
RAPID3	r	0.669	0.296
	p	<0.001	0.113

RAPID3: Routine Assessment of Patient Index Data 3, ESSDAI: The European League Against Rheumatism Sjögren's Syndrome Disease Activity Index, ESSPRI: The European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index

p=0.007). Lissamine green score was negatively correlated with the Schirmer test and BUT (r=-0.484, p=0.007, and r=-0.507, p=0.004, respectively). Despite there was high compliance among these three scales evaluating eye involvement, these scales did not appear to correlate with the ESSDAI, ESSPRI, and RAPID3 scores that assess the global activity of the disease. The mean age was significantly higher in patients with the Schirmer test ≤5 mm compared to the patients with >5 mm (55.6±6.9 vs 47.6±8.5 years, p=0.044).

DISCUSSION

SS is a systemic autoimmune disease that primarily affects the exocrine glands (mainly the salivary and lacrimal glands) and results in the severe dryness of mucosal surfaces, principally in the mouth and eyes. This disease predominantly affects middle-aged women, but can also be observed in children, men, and the elderly. The clinical presentation of SS is heterogeneous and can vary from sicca symptoms to systemic disease (characterized by peri-epithelial lymphocytic infiltration of the affected tissue or the deposition of the immune complex) and lymphoma. The mechanism underlying the development of SS is the destruction of the epithelium of the exocrine glands, as a consequence of abnormal B cell and T cell responses to the autoantigens Ro/SSA and La/SSB, among others. Diagnostic criteria for SS include the detection of autoantibodies in patient serum and histological analysis of biopsied salivary gland tissue (1). Therapeutic approaches for SS include both topical and systemic treatments to manage the sicca and systemic symptoms of the disease. SS is a serious disease with excess mortality, mainly related to the systemic involvement of the disease and the development of lymphomas in some patients. Knowledge of SS has progressed substantially, but this disease is still characterized by sicca symptoms, the systemic involvement of disease, lymphocytic infiltration to exocrine glands, the presence of anti-Ro/SSA and anti-La/SSB autoantibodies, and the increased risk of lymphoma in patients with SS (1). Disease activity and damage index are two different antitheses used in the follow-up and evaluation of diseases. Conceptually, activity refers to the reversibility of the process, while damage is an irreversible process associated with a permanent loss of function of the organ or system. Severity, on the other hand, means that there are increased reversible and irreversible changes caused by the disease in a particular organ or tissue (12). In SS, it is difficult to detect disease activity. Comorbid psychosomatic diseases affect the set detecting global disease activity. On the other hand, the activity of glandular involvement and global disease activity are not with compliance (6). Indices such as the SS Disease Activity Index and Sjögren's Clinical Activity Index have been used regionally to measure disease activity in patients with SS with systemic symptoms. Because to the fact that these indices have been developed in a limited number of patients and in a single country, two separate indices have been developed aimed at evaluating two different aspects of the disease. The ESSDAI index has been developed for systemic findings, and the ESSPRI index has been developed for patients' symptoms (12,13).

The ESSDAI is a systemic disease activity index measuring disease activity in patients with SS. The ESSDAI is a physician-oriented outcome measure. With the growing use of the ESSDAI, some domains appear to be more challenging to rate than others. The ESSDAI is now in use as a gold standard to measure disease activity in clinical studies, and as an outcome measure, even a primary outcome measure, in current randomized clinical trials. Therefore, ensuring an accurate and reproducible rating of each domain, by providing a more detailed definition of each domain, has emerged as an urgent need. The ESSDAI includes 12 domains (i.e., organ systems: Cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, lymphadenopathy, and biological) (6). ESSPRI is used to evaluate dryness, fatigue, and pain symptoms, and their impact on the disease. ESSPRI is a patient-administered questionnaire that evaluates dryness, fatigue, and pain, and each component is measured with a single 0-10 numerical scale. A score of 0 indicates the lowest disease activity (7). ESSDAI and ESSRI have been used and evaluated in numerous studies. It has also been shown that both the ESSDAI and ESSRI scores improve significantly after treatment. However, it has been found in studies that the correlation between ESSPRI and ESSDAI is weak (14). Additionally, various activity parameters have been developed according to the specific area of involvement, such as drynessand fatigue. For example, indices such as the Functional Assessment of Chronic Illness Therapy or Fatigue Severity Scale are used for fatigue. Due to the extreme heterogeneity of clinical features in PSS, the search for a new index that can combine the assessment of systemic disease activity, subjective symptoms, glandular function, and serological parameters continues (15). RAPID3 is an index, which includes only the three patient-reported measures from the RA core set physical function, pain, and patient global assessment each scored 0-10, for a total of 0-30. RAPID3 was developed initially for feasibility in routine care, as the patient provides the data while in the waiting area (8). In clinical studies, RAPID3 correlates with the Disease Activity Score 28 (DAS28) and the Clinical Disease Activity Index (16,17). Furthermore, patient self-report questionnaires have higher reproducibility than physician-performed joint counts (18). The correlation of the ESSPRI index

and RAPID3 score in our study may be because both indices are patient-oriented outcome criteria. On the other hand, the lack of correlation between ESSDAI and RAPID3 may suggest that the RAPID3 score is weak in the evaluation of systemic findings.

Study Limitations

The fact that the number of patients is small and no other comparable study group is included is the limitations of our study.

CONCLUSION

ESSDAI and ESSPRI are the main activity scores used in SS. RAPID3 has previously been used in RA, and data in SS are limited. We wanted to test the usability of RAPID3 in our study. In conclusion, these results suggest that RAPID3 can be useful for detecting disease activity in primary SS.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Fırat University Ethics Committee (decision no: 01, date no: 24.02.2015).

Informed Consent: Patient consent form was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S.A., Z.Ö., O.Ç., N.G., Concept: M.S.A., B.Ö., N.G., A.K., Design: M.S.A., B.Ö., A.K., Data Collection or Processing: M.S.A., Z.Ö., S.Ç., Analysis or Interpretation: M.S.A., Z.Ö., A.K., Literature Search: M.S.A., Writing: M.S.A.

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CASE REPORT AND LITERATURE REVIEW

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A CASE OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY ASSOCIATED WITH SYSTEMIC SCLEROSIS SUCCESSFULLY TREATED WITH RITUXIMAB

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Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare subtype of peripheral neuropathy and it may be accompanied by connective tissue disease (CTD). Although there are very few case reports of CIDP associated with CTD, to our knowledge, no case related to systemic sclerosis has been reported in the literature. A 50-year-old male patient who had been followed up by the neurology clinic with a diagnosis of CIDP for 2 years was referred to us with newer onset skin stiffness, Raynaud's phenomenon, swelling and pain in the joints of the fingers. With a detailed evaluation, the patient was diagnosed with systemic sclerosis and the CIDP was considered to be associated with systemic sclerosis. The patient's neurological findings improved with rituximab treatment in addition to corticosteroid.

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, systemic sclerosis, rituximab

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare and acquired immune-mediated neuropathy and the incidence of CIDP is estimated to be 1 in 100,000 persons (1,2). Generally, it is manifested by proximal and distal symmetrical weakness accompanied by sensory complaints with a progressive course for more than 8 weeks (2). The diagnosis of CIDP is based on clinical findings and signs of demyelinating changes in electro-diagnostic tests (2). The cause of CIDP is an autoimmune process consisting of humoral and cellular immunity, with an unknown trigger in most cases (3). CIDP can be observed during many connective tissue diseases, particularly in systemic lupus erythematosus (SLE) and Sjogren syndrome before or after the onset of symptoms (3).

Systemic sclerosis is an autoimmune connective tissue disease leading to fibrosis in the skin, internal organs, and vessels (4,5). The pathogenesis of the disease consists of vasculopathy, immune system activation, and diffuse fibrosis (5). The diagnosis of the disease is generally based on clinical findings, however systemic sclerosis-associated antibodies and nailfold capillaroscopy also support the diagnosis (5). Peripheral neuropathy associated with systemic sclerosis is a known manifestation, but CIDP has not previously been reported during systemic sclerosis. Here, we report a case of systemic sclerosis who presented with CIDP.

CASE REPORT

A 50-year-old male patient was admitted with the complaints of weakness and numbness in both the legs and arms, inability

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to walk without support, and joint pain. The patient had worked in the manufacturing of glass bottles with occupational silica exposure for many years. Two years ago, he started to have difficulty in swallowing, sitting, and climbing stairs, and inability to walk without support. Patient was evaluated by the neurology department and no pathology was detected in the lumbar puncture examination. Electromyelography (EMG) revealed mixed type sensorimotor polyneuropathy and he was diagnosed with chronic inflammatory demyelinating polyneuropathy. Intravenous immunoglobulin (IVIG) therapy of 2 gr/gr monthly was started. The patient was followed up for 2 years in the neurology clinic with monthly IVIG treatment. Then, he was referred to us with the skin stiffness, Raynaud's phenomenon, swelling and pain in the joints of the fingers started a few months ago. On his physical examination, he could not stand without support and could not move alone. Muscle strength was 4/5 in both the upper limbs and 3/5 in the lower limb. Raynaud's phenomenon on the hands and feet, telangiectasia on the face, stiffness and redness of the skin of the hands, sclerodactyly, bilateral arthritis of metacarpophalangeal joints, proximal interphalangeal joints and wrists were detected. Antinuclear antibody and anti-Scl-70 antibody were positive. Computed tomography of the thorax revealed ground glass opacity compatible with non-specific interstitial pneumonia. The control EMG findings were compatible CIDP. The patient was diagnosed with CIDP associated with systemic sclerosis and methylprednisolone at 8 mg/day and 1 course of rituximab (1,000 mg 2 doses, 15 days apart) were given as treatment. At the control examination of the patient after 2 months, he could walk alone without any support, muscle strength was found to be 5/5 in both the upper and lower extremities, and no arthritis was found.

DISCUSSION

CIDP is formed as a because of the influence of environmental and genetic triggers (6). Despite the paucity of cohort studies in the literature, infection is the main trigger for developing CIDP (6). CIDP can be observed during many bacterial and viral diseases. Besides, the polyautoimmunity phenomenon is also a concept that should be mentioned in the cause of CIDP, suggesting an increased risk of of developing another autoimmune diseases in a patient with an autoimmune disease. It is common for patients diagnosed with CIDP to be accompanied by an autoimmune disease at the time of diagnosis or at later stages during the disease. In the literature, many cases of CIDP associated with various autoimmune diseases, especially with multiple sclerosis, myasthenia gravis, SLE, Sjögren's syndrome, rheumatoid arthritis, Hashimoto's thyroiditis, Graves' disease, type 1 diabetes mellitus, vitiligo, primary biliary cholangitis, and autoimmune hepatitis, have been reported (6). The neurologic involvement in systemic sclerosis contains the central and peripheral nervous system, but the central nervous system involvement is rare. Peripheral neuropathy is not rare in patients with systemic sclerosis with a prevalence of 27.37% (7). In peripheral nervous system, cranial, peripheral, cutaneous, autonomic, and entrapment neuropathies can be detected (7,8). During systemic sclerosis, trigeminal neuralgia, peripheral sensorimotor polyneuropathy, carpal tunnel syndrome are often observed (8). However, when we look at the literature, no case of CIDP associated with systemic sclerosis has been reported to date. There are options such as glucocorticoids, IVIG, rituximab, plasmapheresis for treating CIDP (9). If there is an underlying cause or disease, treatment should be administered for it as i ur case.

CONCLUSION

CIDP may be one of the rare neurological involvement patterns of systemic sclerosis and the underlying systemic sclerosis should be considered in both the evaluation and management of the patient to control findings of CIDP effectively.

Ethics

Informed Consent: We written informed consent for publication of clinical details was obtained from the patient. No ethics board approval was required for this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., C.B., Concept: C.B., Design: C.B., Data Collection or Processing: M.K., C.B., Analysis or Interpretation: C.B., M.K., Literature Search: M.K., R.D., C.B., Writing: M.K., R.D., C.B.

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CASE REPORT AND LITERATURE REVIEW

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A TRIANGLE: RHEUMATOID ARTHRITIS, MYASTHENIA GRAVIS AND ANTI-TNF. GOOD NEWS OR BAD NEWS? LONG -TERM FOLLOW-UP: CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies. Inhibitors of tumor necrosis factor (TNF)-alpha are widely used for treating RA. However, prolonged use of these agents has been associated with induction some autoimmune disease. Here, we have shown that anti-TNF drugs used in long-term follow-up of two patients diagnosed with both RA and myasthenia gravis, are safely.

Keywords: Rheumatoid arthritis, myasthenia gravis, tumor necrosis factor

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies (particularly to rheumatoid factor and citrullinated peptide) (1). Tumor necrosis factor (TNF) is a proinflammatory cytokine that plays a role in the pathogenesis of many chronic inflammatory autoimmune diseases, especially in RA. Anti-TNF-alpha agents inhibit the proinflammatory effect and reduce the activity of the disease. As a result with this mechanism improves the RA and many other autoimmune disease symptoms (2). Despite these important clinical benefits, long-term use of biological agents such as TNF Alpha inhibitors may trigger antibody development, and various autoimmune events may occur (3). Some demyelinating diseases are activated during the use of biological agents. Although biological agents are contraindicated in demyelinating diseases of the central nervous system, such as multiple sclerosis, there is no more information and advice about the relationship between anti TNF-alpha agents and prognosis of myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction. Here, we reported long-term follow-up results of two patients diagnosed with both RA and MG, with similar cases in the literature.

CASE REPORT

Case 1

A 58-year-old woman was admitted to the neurology clinic in 1999 with asymmetric ptosis, weakness in both arms and legs, inability to hold the neck, and speech disorders. In her neurological examination, it was determined that tetraparesis, bilateral asymmetric ptosis, binocular diplopia after physical effort, and nasone speech, able to count to 20 before his voice became inaudible. An electromyography (EMG) study

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was performed from the extraocular and extremity muscles, and a significant decrement was detected. The patient was diagnosed with MG and given intravenous immunoglobulin (IVIG). Pyridostigmine 3x1 and methylprednisolone 10 mg/day were started. The patient underwent chest computerized tomography (CT) for possible thymoma, but no thymoma was detected. The patient undergoes annual routine checks for MG. After 9 years, pain and swelling of the hand and wrist joints started. On the rheumatological examination, symmetrical arthritis was detected. Her blood tests revealed rheumatoid factor (195 IU), elevated sedimentation (72 mm/h), C-reactive protein (45 mg/L) and anticyclic citrullinated peptide antibodies (450 RU/mL). According to the current clinic features and values, the patient was diagnosed with RA and treatment was started as methotrexate 15 mg/week, sulfosalazin 2 g/day, and hydroxychloroquine 400 mg/day. Although joint complaints decreased but not fully healed, therefore etanercept was added to the current treatment after 3 months. Adalimumab was added after the patient, who had been in remission for about 3 years, showed an exacerbation after her complaints. The patient is still under adalimumab treatment and has been in remission for 7 years. While the patient was taking available biological agents for RA, no myasthenic crisis or increase in the MG clinic was observed. He received only once IVIG treatment at the time of diagnosis. Until now, the dose of oral pyridostigmine did not exceed 3 pieces/day. Oral steroid doses were consistently taken at 5 or 10 mg doses. Routine checks for MG were performed on average twice a year for 20 years. During this period, he did not have any complaints such as increased extremity weakness, binocular diplopia, fall in the eyelid, swallowing and speech impairment, and breathing difficulties.

Case 2

A 35-year-old woman was admitted to the neurology clinic in 2009 with unilateral ptosisand weakness of both arms and legs. In her neurological examination, it was determined that tetraparesis, asymmetric ptosis, and diplopia after physical effort, able to count to 15 before his voice became inaudible, nason speech and increase ptosis after the eye strain test. An EMG study was performed from the extraocular and extremity muscles, and a significant decrement was detected. The patient was diagnosed with MG and given IVIG. Oral pyridostigmine 5x1 and methylprednisolone 10 mg/day were started. The patient underwent a chest CT for a possible thymoma. The chest CT scan showed a neoplastic anterior mediastinal mass, compatible with timoma. The patient underwent thymectomy surgery. The clinic of MG is stable with the current oral treatmen; after 3 years, pain and swelling in the hand joints started. Her blood tests revealed rheumatoid factor (340 IU), elevated sedimentation (65 mm/h), C-reactive protein (93 mg/L) and anticyclic citrullinated peptide antibodies (210 RU/mL). According to the current clinic features and laboratory values, the patient was diagnosed with RA and treatment was started as methotrexate 15 mg/week, hydroxychloroquine 200 mg/day, and prednisolone 5 mg/day. After his complaints were not exceeded, approximately 5 months later, adalimumab was added to the treatment. Methotrexate was stopped because it was nauseous. Sulfosalazin was added instead. The patient is still under treatment as adalimumab 40 mg every 15 days, hydroxychloroquine 200 mg/day, and methylprednisolone 2 mg/day. Due to MG, pyridostigmine takes 4x1 in maintenance therapy. No myasthenic crisis and worsening in the MG clinic have been observed for 11 years.

DISCUSSION

Here, we have shown that anti-TNF agents are safe in two patients with RA and MG, and that they do not cause any exacerbation related to MG.

Despite these important clinical benefits, long-term use of biological agents such as TNF-alpha inhibitors, may trigger antibody development and relieve various autoimmune events (3). Although there are many studies showing that anti TNF-alpha agents predispose to demyelinating diseases in the central nervous system, there is not much data on the relationship between antibody-mediated autoimmune diseases such as MG. MG is an autoimmune disease of the neuromuscular junction caused by antibodies that attack the components of the postsynaptic membrane and disrupt neuromuscular conduction. As a result leads to weakening and fatigue of the skeletal muscle (4). Because autoimmune diseases of the neuromuscular junction are antibody mediated, B lymphocytes play an important role in this process. B lymphocytes need T lymphocytes to become sensitive to target antigens at the neuromuscular junction and to produce high-affinity antibodies. Therefore, both humoral and cellular immune systems must interact mutually for developing autoimmune neuromuscular junction diseases (5). Gradolatto et al. (6) showed that immunoregulation defects observed in MG patients were caused by both Treg and Tconv cell disorders and was central to many proinflammatory processes, including TNF-alpha. Additionally, it was revealed by the polymerase chain reaction study that TNF-alpha plays a role in the pathogenesis of MG disease (6). Duan et al. (7) revealed that IL-6 and TNF-alpha are associated with MG pathogenesis and immunoregulation. Additionally, this study demonstrated that IL-32 induced TNF-alpha, which is central to experimental autoimmune MG induction and development (7). In a prospective pilot study

by Erdem Tüzün et al. (8) reported improvement in steroid-dependent MG patients after treatment with etanercept. In this study, it was found that anti-TNF agents increased the level of circulating immune complexes without changing plasma anti-ach receptor antibody levels (8). In line with the findings that support the role of TNF-alpha in the etiopathogenesis of MG, there are a limited number of studies showing that anti-TNF agents may be a treatment alternative in MG. In contrast, there are a few rare studies with case studies showing that anti-TNF agents can trigger MG. In a case reported by Fee et al. (9), they presented a patient who developed MG while receiving etanercept treatment and who developed MG symptoms related to etanercept as the first case in the literature. However, etanercept came to the fore as an alternative agent recommended for treating MG in the coming years (9). In another case report showing that TNF-alpha blockers can trigger MG, methotrexate, and cyclosporine were started in a patient diagnosed with psoriatic arthritis. After a while, these agents were discontinued and etanercept was applied for 10 years. Then, ustekinumab was given. Thymoma and myasthenic symptoms appeared 6 months after ustekinumab was started. After these agents were discontinued and methotrexate and prednisolone were replaced, myasthenic symptoms improved (10). There are potential side effects of long-term immunosuppressant agents in MG. It has been supported by a limited number of studies that TNF-alpha inhibitors can be preferred instead of these immunosuppressant drugs in MG (11). However, it has been reported in several cases that TNF-alpha blockers used in various autoimmune chronic inflammatory diseases can trigger another autoimmune disease, such as MG (12,13) (Table 1).

Table 1. The features of cases associated with MG during the use of biological agents for rheumatological disease

	Nicocia et al. (10)	Fee et al. (9)	Angelucci et al. (12)	Pelechas et al. (13)	Bixio et al. (11)	Our case 1	Our case 2
Age/gender	50/M	66/M	68/F	42/F	1. case: 48/M 2. case: 55/F 3. case:54/F	58/F	35/F
The type of rheumatological disease and disease duration	PSA 15 years	RA Unknown	RA comorbidity: Crohn's disease, uveitis	RA 2 years	1. case: RA 2. case: RA 3. case: RA	RA 11years	RA 8 years
Presence of MG before rheumatological disease and duration	No	No	No	No	1. case: No 2. case: No 1. case: Yes, 22 years	Yes 20 years	Yes 11 years
Type of autoantibody and serum levels	Unspecified	Unspecified	Unspecified	Anti-CCP: -RF:+	1. case: Anti-CCP: + RF: + 2. case: Anti-CCP: + RF: - 1. case: Anti-CCP: + RF: +	Anti-CCP: + RF: +	Anti-CCP: + RF: +
The thymus	Thymus hyperplasia	Normal	Normal	Normal	1. case: Normal 2. case: Normal 3. case:Thymus hyperplasia and thymectomy	Normal	Thymus hyperplasia
Myasthenic symptoms or MG crisis during biological agent treatment	Yes (4 years after beginning etanercept treatment)	Yes (occured during etanercept treatment)	None	Yes (18 month after beginning adalimumab treatment)	1. case: None 2. case: None 3. case: None	None	None
Possible trigger agent for MG	Etanercept	Etanercept	None	Adalimumab	1. case: None 2. case:None 3. case: None	None	None
Biological and other agent treatment for rheumatological disease	MTX cyclosporine etanercept ustekinumab	Etanercept	Infliximab and adalimumab	MTX prednisone adalimumab	1. case: MTX, UPA 2. case: LEF, UPA 3. case: GC, HCQ, CTZ-peg	Etanercept: 3 years Adalimumab: 7 years	Adalimumab: 7 years

MG: Myasthenia gravis, RA: Rheumatoid arthritis, CCP: Cyclic citrullinated peptide, MTX: Methotrexate, UPA: Upadacitinib, LEF: Lymphoid enhancer factor-1, RF: Rheumatoid factors, HCQ: Hydroxychloroquine, CTZ: Certolizumab ,F: Female, M: Male

CONCLUSION

In both cases we presented, our patients were followed for more than 10 years with the diagnosis of RA. The diagnosis of MG was initially present in both of our patients. Our patients use etanercept and adalimumab because of RA. In both of our patients, the MG clinic has been stable for many years, and no myasthenic crisis was encountered in this process. In both of our patients, there was no clinical deterioration in MG due to the TNF-alpha blockers used for RA. Our cases show that TNF-alpha blockers are safe in MG disease, even if they are used for many years. Because the number of our cases is few, more comprehensive and extensive studies are needed to prove the accuracy of this hypothesis. Additionally, our patients were given agents such as low -dose steroids and methotrexate in addition to TNF-alpha blockers for RA. The use of these agents may be related to the stable clinic of MG clinics in our patients. As a result, we can say that TNF-alpha blockers can be used safely in MG, which is based on 2 cases we have followed for many years. In addition to the limited number of studies demonstrating that TNF-alpha blockers may be included in the treatment protocol in the long term in MG in the following years, there is a need for more comprehensive and controlled studies involving the larger population in this regard. In addition to the limited number of studies showing that TNF-alpha blockers may be included in the treatment protocol in the long term in MG in the following years, the opposite has been shown in some cases where these agents trigger MG. Therefore, controlled studies involving a wider and larger population are needed.

1- Anti-TNF agents can be used safely in the long term in patients that have additional diagnosis such as myasthenia gravis.

2- Anti-TNF agents do not significantly worsen symptoms of myasthenia gravis disease in the long term.

3- There are very few studies investigating the effects of the use of anti-TNF agents on the course of myasthenia gravis disease.

Ethics

Informed Consent: Patient consent has been obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., F.A., H.E.Ö., B.K., Design: E.K., F.A., H.E.Ö., B.K., Data Collection or Processing: E.K., F.A., H.E.Ö., B.K., Analysis or Interpretation: E.K., F.A., H.E.Ö., B.K., Literature Search: E.K., F.A., H.E.Ö., B.K., Writing: E.K., F.A., H.E.Ö., B.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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IMAGE ARTICLE

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RICH SKIN MANIFESTATIONS IN DERMATOMYOSITIS

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Keywords: Dermatomyositis, skin, muscle weakness

INTRODUCTION

A 49-year-old female patient presented with complaints of pain and weakness in the shoulders, arms, and legs. About 2 weeks after the complaint of pain and weakness, purplish-red discolorations started on her face, around her eyes, and later on her neck and upper chest. She presented to us with purplish discoloration around her eyes (Figure 1A) and diffuse red-purple discoloration on the neck and upper chest. Additionally, raised lesions of pink-purple skin were observed on the extensor surfaces of the proximal interphalangeal joints on the hands, elbows, and knees (Figure 1B,1C). Laboratory examination revealed creatine kinase (CK): 549 U/L, aspartate aminotransferase: 61 U/L, alanine aminotransferase: 58 U/L, creatinine: 0.49 mg/dL, erythrocyte sedimentation rate: 54 mm/hour, antinuclear antibodies (ANA), and ANA subgroups were negative.

In magnetic resonance imaging, signal increase in T2 images and local contrast enhancement in post-contrast series were observed in bilateral thigh muscles (Figure 2A, 2B). In view of current clinical and laboratory findings, the patient was diagnosed with dermatomyositis and was started on methyl prednisolone 120 mg/day (intravenous), hydroxychloroquine 2x200 mg, methotrexate 15 mg/week (peroral), folic acid 5

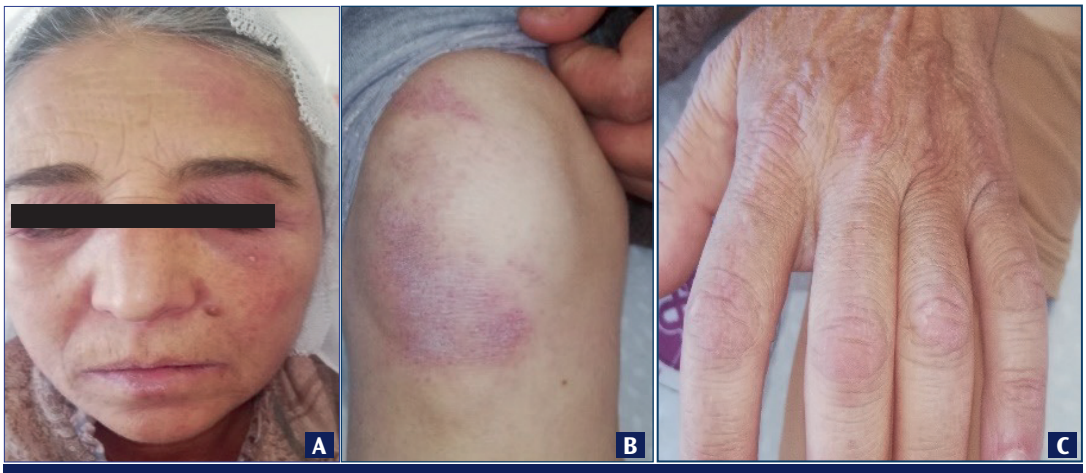

Figure 1. A. Bilateral lilac discoloration of the eyelids, B. Violaceous skin changes over the knees (Gottron sign), C. Gottron papules on the finger joints

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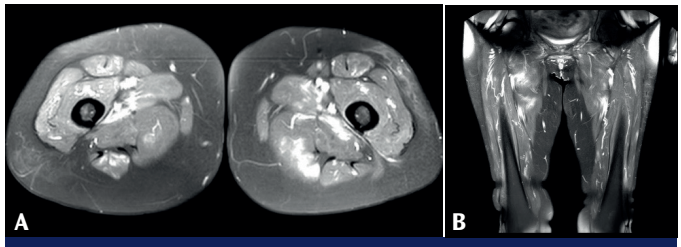
mg/week, and calcium/vitamin D supplementation. On the 5th day of her treatment, she regressed to CK: 161 U/L and lactate dehydrogenase: 277 U/L. The patient, whose complaints of muscle weakness decreased and skin lesions started to regress, was discharged with a steroid dose reduction schedule, with the recommendation of outpatient control (1).



Figures 2A-B. Bilateral muscular edema of the thigh muscles

Ethics

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., A.K., Concept: S.G., Design: S.G., A.K., Data Collection or Processing: S.G., A.K., Literature Search: S.G., Writing: S.G.

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