e-ISSN: 2791-9250

DAHUDER MEDICAL JOURNAL

Volume 2 · Issue 1 · January 2022

DAHUDER MEDICAL JOURNAL

Available at http://dergipark.org.tr/en/pub/dahudermj

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Biotechnology

DAHUDER Medical Journal
e-ISSN: 2791-9250

A review on the toxic effects of medicines used in corona virus disease 2019 (Covid-19) treatment

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ABSTRACT

Objectives: The novel coronavirus disease 2019 pandemic is affecting all around the world, particularly healthcare systems. The most critical problem for the COVID-19 infection as an emerging acute respiratory disease is the lack of effective methods to control and treat the disease. To date, there is no specific therapeutic agent approved by the FDA, so treatment options are limited. There are more than 4034 interventional studies in progress listed in clinicaltrials.org (Access date: 21.12.2021). This number was 900 approximately in December 2020. These intensive studies, which have increased fourfold, are to find a safe and effective treatment method. Since absolute therapy has not been standardized globally, the treatment approach varies from country to country and even from hospital to hospital. In addition to the vaccine studies that have been finalized and the vaccines are available for use, additional studies are underway for existing drugs that can prevent this disease or improve outcomes for COVID patients. The potential toxicity of the drugs chosen for the treatment is one of the more critical limiting factors. Although the side effects of previously approved medicines are known, studies are needed to determine the side effect profiles for newly approved products such as remdesivir.

In this review, we gathered the adverse and toxic effects of medications used against COVID-19 treatment according to the COVID guideline published by the Scientific Advisory Board of the Ministry of Health of Turkey.

Keywords: Coronavirus disease 2019 (COVID-19), SARS-CoV-2; medicines, remdesivir, anakinra, tocilizumab, favipiravir, hydroxychloroquine, convalescent plasma, toxic effects, adverse effects

The coronavirus disease, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) latter that occurred in Wuhan, China in late December 2019, has spread rapidly to almost the whole world. [1] COVID-19 outbreak has spread to Turkey on March 2020, while the World Health Organization (WHO) declared the COVID-19 pandemic. As soon as the disease began to appear in Turkey, the Scientific Advisory Board was established, and they published an actively updated guideline for treatment of patients across the country. In the first edition of the guideline, the recommendations were focused on controlling the possible coinfections and cytokine storm management. According to increasing evidence about the endothelial invasion of the virus and the increased thromboembolic effects of the disease, anti-aggregate, and anticoagulant drugs were included in the treatment program. [2]

The medications for COVID treatment are limited, and clinical studies are not enough. The phase trials have not reached the optimum level; this state brings us a dilemma, to use or not to use these medications.

Received: *December 28, 2021****; Accepted:*** *January 11, 2021****; Published Online:*** *January 29, 2022*

How to cite this article: *Özlü A, Taner G, Koca N. A review on the toxic effects of medicines used in corona virus disease 2019 (Covid-19) treatment. DAHUDER M J 2022, 2(1):1-10.*

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The last example of this situation is Remdesivir, a nucleoside analog pro-drug. Wang et al., conducted a randomized, double-blind, placebo-controlled multicenter trial from China, for evaluating the efficiency of Remdesivir. [3] They stated that no clinical improvement was achieved with Remdesivir treatment and stopped the trial because of the adverse effects. On the other hand, FDA approved Remdesivir for COVID treatment. [4] By the way, there is an urgent need for more phase trials and clinical outcomes for all medicines using for the COVID treatment.

According to the Turkish Scientific Advisory Board, COVID guideline, hydroxychloroquine, oseltamivir, favipiravir, lopinavir/ritonavir, azithromycin, tocilizumab, and low molecular weighted heparins are used frequently. The toxic profile of medications used in COVID treatment should not be ignored. Since these drugs are on the market with different indications for years, there are enough data for the safety profiles. Particularly, adverse, and toxic effects of hydroxychloroquine and chloroquine are well known. Although remdesivir, favipiravir, and tocilizumab are relatively new agents, their toxicity and side effects are also well known not as much as hydroxychloroquine and chloroquine.

A broad-spectrum antibiotic azithromycin is not indicated for the viral infections, and there are not well-controlled, prospective, randomized clinical trials for proving its therapeutic effect in COVID-19. Despite the side effects, convalescent plasma therapy (CPT) is also used in the treatment of severe cases. It is known as classic adoptive immunotherapy, and there are many reports where the CP has successfully been used for the treatment of infectious diseases and other coronavirus outbreaks. In this study, we reviewed the databases and literature to consolidate information about the medications and therapeutics used for COVID treatment.

METHODS

We reviewed the literature using ScienceDirect, UptoDate, Clinicalkey, and Google Scholar search engine with the search terms included COVID treatment, pharmacological treatment of COVID, and toxicity of medications used for COVID treatment. We excluded preprint articles and included case reports. Other articles regarding the review of citation references have also been identified.

Medications used in COVID

Hydroxychloroquine and chloroquine

Quinine derivatives are using since the 1950s for malaria. They have been used for some autoimmune disorders by their immunosuppressive properties. They are also in WHO's Essential Drug List, and their side effects are well known due to their usage for 70 years. A 4-aminoquinoline derivative, hydroxychloroquine, a less toxic molecule from chloroquine, is synthesized by beta hydroxylation of chloroquine. [5]

Colson et al., stated that chloroquine might be effective for COVID based on their in vitro study. They said chloroquine has multiple activities for blocking viral replication, fusion, and uncoating and has a broad antiviral spectrum. It seems to be cost-effective already. By the way, in their opinion, chloroquine could be o good treatment option for the COVID. [6, 7]

The hydroxychloroquine and chloroquine treatment included in the Turkish COVID guideline since the beginning of the pandemic. The guideline recommended hydroxychloroquine treatment 400 mg bid for the first day and 200 mg bid for the following four days maximum of ten days. [2] In addition to the antiviral effects of chloroquine, it inhibits some biochemicals causing cytokine storms like IL-6 and TNF and thought to have positive effects for cytokine storm 8. But in the current treatment protocol, hydroxychloroquine and chloroquine are not recommended for first-line treatment. But, because of the past treatment approach of the Turkish Scientific Advisory Board, we've included adverse effects of these medicines.

Favipiravir

Favipiravir (T-705) is a pro-drug of a purine nucleotide, favipiravir-ribofuranosyl-5′-triphosphate. After metabolization, the active agent inhibits the RNA polymerase. Favipiravir has some preclinical outcomes for Ebola and influenza treatment 9. Favipiravir treatment is not recommended as the first line of treatment and is reserved for the severe COVID pneumonia. According to the Turkish COVID guideline, favipiravir treatment is started with 1600 mg bid for the first day and continue 600 mg bid for the following four days. [2]

Favipiravir treatment for COVID is evaluated on Phase III PRESECO study. This study has important results for understanding the efficacy of favipiravir for mild to moderate COVID patients. The data from this randomized clinical study has shown no significant effect on treatment. [10] There's not a different approach for favipiravir in Turkish Treatment Protocol

and continues to be used routinely in treatment based on guideline

Tocilizumab

Tocilizumab is a humanized monoclonal antibody that inhibits the IL-6 receptor. FDA approved it for the treatment of severe rheumatoid arthritis. When TNF-blockers have failed or contraindicated for the treatment, tocilizumab may be a good alternative. In addition to rheumatoid arthritis, tocilizumab is approved for cytokine syndrome caused by chimeric antigen receptor (CAR) T cell treatment. [11] Although there is not enough data for COVID treatment, tocilizumab thought to be beneficial for the management of the cytokine storm as an adjunctive agent. The Scientific Advisory Board advises tocilizumab treatment, particularly in patients who develop macrophage activation syndrome (MAS) with 8 mg/kg dose (up to 800 mg/kg). Depending on the severity of the patient's symptoms, 400 mg/kg or 800 mg/kg can be given intravenously as the first dose. In the case of giving the first dose as 400 mg/kg, based on clinical and laboratory responses, 200-400 mg dose may also be given within 12-24 hours. [2]

Remdesivir

Remdesivir is a nucleotide analog antiviral medicine approved for COVID-19 treatment based on preclinical studies. It's a prodrug has a broad antiviral spectrum against RNA viruses. This effect comes from inhibiting viral RNA dependent RNA polymerase and mitochondrial RNA polymerase weakly. [12] Although, remdesivir treatment is not recommended in Turkish Guideline briefly, it's been used in clinical practice.

Anakinra

Anakinra is a non-glycosylated human interleukin-1 receptor antagonist that uses for cytokine storm in COVID treatment. Before this repurposing, it has been used for rheumatoid arthritis and other inflammatory diseases.

In a systematic review that compiled by Kyriazopoulou et al., 2021, it's stated that anakinra seems to be an alternative for hospitalized COVID-19 patients at the presence of hyper inflammation. [13]

In another meta-analysis conducted by concluded that anakinra treatment could be effective for patients requiring a mechanical ventilator. [14] In opposite to some positive results, because of insufficient evidence, NIH does not recommend using Anakinra in COVID-19 treatment. On the other hand examined 20 cases and 20 control groups .[15] The results of the study expressed that anakinra treatment was not effective for tocilizumab-resistant severe COVID-19 patients.

Anakinra uses in COVID-19 related macrophage activated syndrome when there is not enough response to glucocorticoid treatment. The administration dosage is 100 mg subcutaneous once or twice a day or 200 mg intravenously three times a day. The dosage could be increased up to 200 mg every 6 hours. [2]

Lopinavir/ritonavir

Lopinavir/ritonavir is an antiviral combination is used for the HIV treatment in adult and pediatric patients. Both medicines are protease inhibitors, and lopinavir concentration is higher than ritonavir in that combination. [16] There is no scientific evidence to use for COVID treatment, but this combination has been used for SARS and MERS treatment. Although limited available studies that associated reduced mortality and intubation rates with uncertain outcomes. [9] The Scientific Advisory Board recommends Lopinavir/ritonavir combination treatment for just pregnant and children. [2]

Azithromycin

Azithromycin is a macrolide antibiotic that semisynthetic form of erythromycin. It shows a good antibacterial effect on gram-positive and gram-negative organisms. It's a bacteriostatic agent that inhibiting protein synthesis by binding the 50S ribosomal subunit. [17] It is used for the treatment of various bacterial infections, as well as in some inflammatory diseases for its immunomodulatory properties. [18, 19, 20] The usage of azithromycin in COVID treatment is reserved just for hospitalized patients, especially in ICU, due to its possible cardiotoxic effects. [2]

Convalescent plasma

Convalescent plasma (CP) is a biologic product from immune people who had an infectious disease. CP therapy (CPT), classic adoptive immunotherapy, has been applied for the treatment of many infectious diseases. It provides passive immunity by giving neutralizing antibodies to the patient. [21] It has been using for patients with various viral infections, such as SARS, pandemic influenza and severe Ebola virus infection. [22, 23, 24] Shen et al. conducted a trial to determine the effects of CPT for five critically ill COVID and ARDS patients. [25] Despite a limited sample size and study design, they stated that CPT might be useful for critically ill patients. Zhou et al., reported that

early convalescent plasma therapy for influenza and SARS-CoV infection is associated with reduction in viral load and mortality. [26] In Turkey, CPT is applying in many hospitals by gathering plasmas from recovered COVID patients. The Ministry of Health of Turkey publishes a guideline describing all the steps for applying Convalescent Plasma Therapy. [27]

Adverse and Toxic Effects of COVID-19 Therapeutics

Effects of hydroxychloroquine and chloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are in clinical use for several years, so both molecules have a well-established safety profile. [28] They are known as well tolerated molecules in general, but they are also extremely toxic in overdose. Some studies draw attention to serious adverse effects that may occur, even during short courses of treatment. The difference in mechanisms of action both of medicines is not fully understood but hydroxychloroquine reported as less toxic. [29] CQ and HCQ's therapeutic index is narrow so effective dose and toxic dose close to each other. HCQ is administered oral route and metabolized in the liver to three different metabolites by conjugation and alkylation. [30]

Cardiologic side effects of quinine derivatives are known. These medicines can cause ventricular arrhythmias, QT prolongation, torsades de pointes, which may pose a particular risk to critically ill persons. Because of this side effect, HCQ/CQ must be used with caution in patients with congenital long QT syndrome, AV block, heart failure, MI, stroke. [30, 31, 32] Patients using medicines that increase the QT interval must also be considered.

CLQ/HCQ cardiotoxicity includes dysrhythmia, depressive cardiac contraction, and conduction related to hypokalemia due to potassium shift. These cardiologic risks increase with the use of azithromycin. [33] HCQ and azithromycin use together only for inpatients in Turkey because of cardiotoxic side effects.

Antimalarial dependent retinal damage is a toxic effect that can be seen in patients that have ocular diseases. Some of these side effects are vision loss and difficulties, scotomata, and impairment in color perception. In some cases that given HCQ for lung cancer treatment, retinal toxicity was observed within 1-2 years of the treatment. It is suggested to screen patients receiving HCQ for retinal damage [34, 35, 36, 37] In Turkey, HCQ is given to all patients at the beginning of the symptoms, so clinicians must be aware of this side effect for the next two years.

CQ/HCQ metabolized in the liver and eliminated by the kidney, so kidney and/or liver failure may increase these drugs' plasma concentrations. [38] Glucose-6-phosphate dehydrogenase deficiency is a contraindication for HCQ treatment because of increased hemolysis risk. HCQ should not be used in the treatment of breastfeeding, pregnant women, and patients allergic to CQ or HCQ. [22] More than 5 grams of chloroquine dose is associated with ventricular arrhythmias and mortality due to hypokalemia. [39]

Effects of Favipiravir

Favipiravir is available as a pro-drug and in in vivo transformed into its active form, Favipiravir- by cellular enzymes. The active form of Favipiravir inhibits the RNA-dependent RNA polymerase (RdRp) of the influenza virus effectively. This specific mechanism of inhibiting influenza virus RdRp specifically involved in DNA synthesis makes it a good option for the treatment of influenza virus infections. [40, 41] Although Favipiravir does not have the specifications of nucleoside analogs that can give rise to mitochondrial toxicity, its possible harmful effects on that organelle could not be excluded entirely. Its potential toxic effects for mitochondria could not be excluded entirely, as it may act as a useful substrate for human mitochondrial RNA polymerase. [42, 43] Jin et al. pointed out that during clinical studies there are severe cases of toxicity associated with ribonucleoside analogs. [42] They assumed that the active metabolites of toxic ribonucleoside analogs, the triphosphate forms, mistakenly target human mitochondrial RNA polymerase thereby inhibit the mitochondrial RNA transcription and protein synthesis. Some researchers have suggested that pro-drug moiety released from ribonucleoside analogs may cause toxicity. In general, they reported that Favipiravir did not have a typical mitochondrial toxic nucleoside profile in their experiments, but the potential toxic effect on the mitochondria should not be ignored as it is a useful substrate such as 6-methylpurine. [42]

On the other hand, many other factors need to be considered to assess the clinical toleration of the use of polymerase inhibitors for their safety. Clinical data for the favipiravir toxicity is limited, but deductions from reported toxicity of other nucleoside analogs can be used. As with all medicines, one disadvantage of Favipiravir is its low solubility in an aqueous medium, which reduces its in vitro efficacy. [44] It has been reported that metabolic acidosis may occur usually after one month or more of treatment in therapeutic dose. Also, this situation has been observed with acute over-

dose. Nagata et al. indicated that favipiravir has a risk for teratogenicity and embryotoxicity in humans. [45]

Effects of Tocilizumab

Tocilizumab (TCZ) is a monoclonal antibody that inhibits the interleukin-6 receptor. According to experimental and clinical studies, while liver toxicity is less common, an increase in lipids parameters and a decrease in neutrophils and skin infections are more common in groups given TCZ. Morrison et al., stated that clinicians should consider monitoring COVID patients using TCZ for hypertriglyceridemia and acute pancreatitis, as described for rheumatoid arthritis patients using TCZ chronically. [46]

Capra et al. did not observe any side effects in their study that aims to evaluate if tocilizumab reduces mortality in patients with COVID-19 related pneumonia. [47] The known important complications of tocilizumab are intestinal perforations or bacterial infections. But in this study, these adverse effects have not been observed.

Tocilizumab can cause hyperbilirubinemia in rheumatoid arthritis patients because it may inhibit uridine diphosphate glucuronosyltransferase 1A1(UGT1A1)-mediated glucuronidation. This increase is thought to be related to the anti-inflammatory effects associated with UGT1A1 polymorphism. Hepatoxicity related to tocilizumab therapy seems low. Macrophage activation syndrome occurs in approximately 7% of juvenile idiopathic arthritis patients. [48]

Infection is an important risk for tocilizumab, like all immunotherapeutics. The occurrence of infection of tocilizumab is researched, and the infection rates of combination therapy (tocilizumab+methotrexate) slightly higher than monotherapy (just methotrexate) regimens. Nasopharyngitis and upper respiratory infections are commonly reported (5%-8%). The risk of severe infections is increasing with the dose. Cellulitis, pneumonia, diverticulitis, gastroenteritis, and herpes zoster were the most common infections reported. [49]

Hypersensitivity is a risk factor, so it should be used carefully for patients with neutropenia (<500 cells/μL) or thrombocytopenia (<50000/μL). Headache, hypertension, increased AST, infusion-related reactions are common side effects of tocilizumab. [9]

Effects of Lopinavir / Ritonavir

Lopinavir / ritonavir treatment for COVID is an obligatory off-label antiviral therapy because of an emergency. The effectiveness of this combination for COVID has been studied in vitro, and clinical implementation was started through acceptable EC50 value. Although there are some favorable outcomes, more clinical evidence is needed . Besides the treatment efficiency, side effects and toxicities must be considered. Yao et al. conducted a trial compromising 199 severe COVID patients. They stated that lopinavir-ritonavir treatment was not associated with clinical improvement. In this trial, the most common side effects are gastrointestinal side effects like nausea, vomiting, and diarrhea. [50] Respiratory failure, acute kidney injury, and secondary infections were also observed in some clinical studies. [51]

The common side of the antiretroviral therapy is the hepatic toxicity, particularly the hepatitis C virus (HCV) infected people. After the treatment of 120 HIV-infected patients (52% HCV-infected) with Lopinavir (LPV), a possible association with severe liver toxicity incidence and LPV plasma levels has been evaluated. [52] According to this study, the incidence of severe liver toxicity was reported as 1.7% in 3rd months, and the cumulative incidence at 12th months was 4%. The development of severe liver toxicity was associated with HCV coinfection, but not with LPV plasma levels. Acute overdose of protease inhibitors is rare, but over 50 g of lopinavir-ritonavir overdose was generally well tolerated and additionally administered. Ritonavir is a very potent CYP3A4, and this effect can cause dangerous drug-drug interactions. [53]

Lopinavir/ritonavir combination must be applied carefully to the patients with hemolytic anemia because of ribavirin. The changes in complete blood count must be monitored closely, and if hemolytic anemia symptom occurs, treatment cessation or dose changes should be considered. One of common adverse effect of ribavirin is bradycardia. [54]

Effects of Azithromycin

Azithromycin, a macrolide antibiotic that is a derivative of erythromycin. Erythromycin is a well-documented molecule that causes hepatotoxicity. Although azithromycin has a very safe side effect profile, cases related to hepatotoxicity due to azithromycin have been reported. In these cases, azithromycin triggered hepatotoxicity associated with oral or intravenous (IV) administration. In the IV administration of azithromycin, an acute increase in AST and ALT levels was observed. [55] Temporary increases in liver enzymes especially transaminases have also been reported in 1.5% of patients. Liver damage due to azithromycin

occurs 1-3 weeks after the onset of azithromycin and is predominantly hepatocellular. While most patients recover completely, severe skin reactions, chronic injuries, and serious complications leading to death or liver transplantation may occur. [56] Azithromycin is generally well-tolerated, but relatively common side effects (1-5% of patients) include gastrointestinal discomfort, headache, and dizziness.

Research points out that azithromycin therapy may cause cardiotoxicity, and its most important side effects include cardiovascular arrhythmias and hearing loss. On the other hand, macrolide resistance is also a problem like interactions with commonly prescribed drugs. [18] Critical adverse effects include QT prolongation and torsades de pointes, resulting in death. In 2012, the FDA issued a warning using drugs that consider the risk of fatal heart rhythm with a long QT interval and may prolong the QT interval with a history of arrhythmias or uncompensated heart failure.

According to a recent meta-analysis of the unfavorable clinical outcomes for the individual and society, long-term azithromycin treatment in patients with chronic lung diseases has increased resistant bacteria risk of macrolide 2.7 times .[57]

Azithromycin is considered safe for pregnant women, and the pregnancy category is known as the drug B1. However, it can cause diarrhea in babies who are breastfed.

Lane et al., reported that the addition of azithromycin to hydroxychloroquine treatment in COVID could potentially cause heart failure and cardiovascular mortality due to synergistic effects on QT length. Caution should be taken if such a combination is used for the management of COVID. [58]

Effects of Convalescent Plasma

The convalescent plasma treatment that has been used for the many kinds of viral infections is not a new approach. Randomized clinical studies are needed to determine the appropriate dose and treatment duration of this treatment method, whose specific effects are known. Recently, Chen et al., and Zhang et al., stated that patient with viral infection immunity plasma can be used in treatment without serious adverse effects. [59, 60] However, safety and efficacy studies should be conducted to determine treatment efficacy for COVID patients. Ahn et al., state that plasma taken from patients with COVID immunity can be an effective treatment option without serious side effects. [61] Convalescent plasma therapy with systemic corticosteroids can reduce excessive inflammatory response and viral load. Moreover, because of the lack of information about the basic biology of SARS-CoV-2, including the variability of the virus and mutations, locally collected plasma can better reflect the virus circulating in the population and be a viable treatment option. In a meta-analysis using convalescent plasma therapy resulted decreasing viral load and mortality. There's not significant adverse effect also in this study. [62]

Besides all these positive effects, plasma transfusion can also cause some side effects. The most common adverse reactions of CP treatment are tremors, fever, anaphylactic reactions, acute lung injury associated with transfusion, circulatory overload, and hemolysis, etc. [23, 24] Meanwhile, the risk of the human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, and syphilis infections should not be ignored. Transfusion-related circulatory overload (TACO) is now recognized as the most common serious side effect of transfusions. CP will result in a direct infusion of a significant amount of complementary protein and clotting factors not found in purified immunoglobulin preparations. [63] For this reason, this treatment approach is recommended as a last resort to increase the survival rate of severe COVID patients. Therapeutic indications need to be further investigated in randomized clinical trials to improve the optimal dose and duration for the treatment of blood products in COVID-19. [26]

It is stated that adverse reactions of convalescent plasma were not increased compared to controls in ESCMID Guideline. Beside some studies reported higher rates of serious adverse events or a small number of infusion-related adverse events. [64]

Effects of Remdesivir

Veklury, the commercial form of Remdesivir for injection, included some side effects on data sheet. There are some clinical outcomes on its safety profile before usage on COVID. In a study for Ebola treatment, one patient developed fatal cardiac arrest because of loading dose administration of remdesivir. But this fatal effect was attributed on Ebola disease, not usage of remdesivir. In another open level study on severe COVID patients, acute respiratory distress syndrome was observed. Atrial fibrillation and hypotension, hypersensitivity reactions, vomiting and nausea, elevated hepatic enzymes, hematological adverse effects, metabolic side effects were reported some clinical studies. [12]

Drug-drug interactions were also reported for chloroquine and hydroxychloroquine co-usage with rem-

desivir. The data based on in vitro experiments Show that HCQ and CQ may be inhibited antiviral activity of remdesivir.

Adverse event reporting from the ACTT-14 trial and the paper by Yeming Wang and colleagues 8 indicate that there is a low risk of remdesivir causing harm, but knowing whether it has any additive effect in combination with corticosteroids is crucial. [65]

In another cohort study, kidney transplanted patients evaluated for renal safety of remdesivir. The treatment did not cease because of side effects. There is no significant hepatotoxic and nephrotoxic side effects of remdesivir. [66]

There's an interesting study about toxicity evaluation of pharmaceutical forms of remdesivir. The injectable form of remdesivir is thought more nephrotoxic than lyophilized form because of an additive-sulfobutylether-β-cyclodextrin. In this study, a number of 1000 patient evaluated for comparing dosage forms toxic effects. It's concluded that injectable form of remdesivir has no disadvantages comparing to lyophilized form. [67]

In conclusion, remdesivir's safety profile is not completed. It should be known that remdesivir treatment could be cause of multiple organs injuries. [68]

Effects of Anakinra

Because of used in rheumatological disease many years, Anakinra's side effects are known compared to other repurposed medicines. One of the major adverse effects is injection site reactions. Besides that, upper respiratory tract infection, headache, diarrhea, abdominal pain is another side effect. [69] In terms of drug-drug interactions, etanercept and anakinra co-usage caused some serious infections.It's not recommended anakinra and etanercept combinations. [70]

Although Anakinra's side effects in rheumatological diseases are well known, it is thought that the side effect profile will change with the disease when used in COVID treatment. For this reason, Anakinra treatment particular in COVID should be considered. In a meta-analysis, hepatic enzymes and thromboembolic reactions were evaluated. There's not statistically significant relation with these markers and Anakinra treatment. [71]

CONCLUSION

While the studies related to updating for vaccines for coronavirus variants are accelerating in many countries, additional studies are ongoing for existing drugs that can prevent this disease or improve outcomes for patients with COVID. For the treatment of COVID, the assignation of old drugs for use as antiviral treatment is an essential strategy because of controlling the disease in the most immediate way. For some of these candidate drugs, knowledge on safety profile, side effects, posology, and drug interactions are well known. [72] On the other hand, there are limited evidence-based research, so clinicians must be aware of these toxicities during the treatment procedures. It is essential to report adverse effects on pharmacovigilance systems for informing health authorities and clinicians. COVID is a new disease for all countries, so the information .and data about the treatment are changing every day. In this dynamic situation, all parts of the healthcare system must upgrade its treatment applications.

Conflict of Interest

The authors have declared no conflicts of interest in this article.

Abbreviations

CAR: chimeric antigen receptor; CP, convalescent plasma; CPT, convalescent plasma therapy; CQ: chloroquine; HCQ: hydroxychloroquine; ICU: intensive care unit; MAS: macrophage activation syndrome; RdRp, RNA-dependent RNA polymerase; TACO: Transfusion-related circulatory overload; TCZ, Tocilizumab; UGT1A1, uridine diphosphate glucuronosyltransferase1A1-mediated glucuronidation

Authors' Contribution

Study Conception: AÖ,; GT,; NK,; Study Design: AÖ,; GT,; NK,; Supervision: AÖ,; GT,; NK,; Data Collection and/or Processing: AÖ,; GT,; NK,; Statistical Analysis and/or Data Interpretation: AÖ,; GT,; NK,; Literature Review: AÖ,; GT,; NK,; Manuscript Preparation: AÖ,; GT,; NK and Critical Review: AÖ,; GT,;NK.

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Original Article

Internal Medicine

DAHUDER Medical Journal
e-ISSN: 2791-9250

Internal Evaluation of Health Conditions of Super-Elderly People Followed Up and Treated in Internal Medicine Clinics

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ABSTRACT

Objectives: A rise in the geriatric population has resulted from the extension of life expectancy in tandem with development. In this population, the super-elderly plays a significant role. In this study, it was aimed to internally evaluate the health status of super-elderly people who were followed up and treated at the Department of Internal Medicine of Recep Tayyip Erdoğan University.

Methods: The study included 393 patients, 246 women and 147 men, all of whom were over the age of 80. The patient files were scanned retrospectively. The patients' demographics, gender, chronic internal diseases, blood count, biochemical parameters, thyroid function tests, B12, and vitamin D levels were all documented. An appropriate statistical programme was used to analyse the collected data.

Results: In terms of chronic disease and drug use, there was no significant difference between the genders in the evaluation of the patients. There were no differences in blood hemogram values between men and women. Women had higher total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels than men. Vitamin D levels were found to be 13.3 ± 9.83 ng/dl in males, 20.3 ± 24.1 g/dl in females and an average of 15.5 ± 16.0 ng/dl in all patients. Vitamin D levels were found to be low in both men and women.

Conclusion: The majority of patients over the age of 80 have vitamin D deficiency, according to these findings. Vitamin D deficiency, which has been linked to increased fragility, should be monitored in this patient group and supplemented if necessary.

Keywords: Chronic disease, Geriatrics, Super-Elderly

Life expectancy at birth has increased all over the world, including in Turkey, as a result of numerous important developments such as advances in disease treatment, successful combat against infectious diseases, and improved living conditions. As a result, the geriatric population has grown. The rise in the geriatric population has resulted in a rise in chronic diseases among this group. Chronic renal failure, hypertension, diabetes, and heart failure are the most common of these diseases.[1] Women make up the majority of the elderly population. This is due to the fact that women live longer than men.[4] The decrease in fertility, followed by the decrease in deaths, is the primary cause of the increase in the proportion of the elderly population.[5] Almost all organs and systems change as people age. The cardiovascular, gastrointestinal, renal, hormonal, immune, respiratory, and musculoskeletal systems all undergo changes. Many chronic diseases will emerge as a result of these changes.

In many countries, people who are 65 years old or older are considered elderly. According to many

Received: *October 5, 2021;* ***Accepted:*** *January 4, 2022;* ***Published Online:*** *January 29, 2022*

How to cite this article: *Yılmaz E, Ayaz T. Internal Evaluation of Health Conditions of Super-Elderly People Followed Up and Treated in Internal Medicine Clinics. DAHUDER M J 2022, 2(1):11-15.*

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sources, people between the ages of 65 and 74 are considered pre-senile, while those over 75 are considered elderly.[2] As a general rule, anyone who is 80 years old or older is considered super-elderly.[3]

There are few studies on super-elderly people in the literature. The goal of this study was to look into chronic diseases that affect the elderly, the drugs that are used to treat them, and the changes that may occur in blood hemograms, biochemistry parameters, thyroid function tests, vitamin D, vitamin B12 levels and the differences between genders.

METHODS

Outpatients and inpatients aged 80 and up who applied to the General Internal Medicine Clinic of Recep Tayyip Erdogan University's Department of Internal Medicine between 2013 and 2018 were evaluated retrospectively in this study.

The study included a total of 393 patients, 246 women and 147 men. All patients' demographics (age, gender, chronic diseases) and medications, as well as hemograms, blood biochemistry values, vitamin D levels (if checked), and vitamin B12 levels, were recorded. The patients were categorised into two groups based on their gender.

The Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee gave their approval for this study, which was numbered 2018/103 and dated 01/06/2018.

Statistical Analysis

The SPSS 25.5 statistical programme was used to conduct the statistical analyses in this study. In the evaluation of the data, the Chi-square test was used to compare descriptive statistical methods (mean, standard deviation) and qualitative data. A statistically significant value of $p < 0.05$ was used.

RESULTS

The study looked at a total of 393 outpatients and inpatients aged 80 and up who were treated and followed up in our hospital's internal medicine clinic between 2013 and 2018. There were 147 (37.4%) males and 246 (62.5%) females among these patients. Among the total number of patients, 134 (34%) had diabetes, 302 (76.8%) had hypertension, 230 (58.5%) had chronic kidney disease, and 248 (63.1%) had congestive heart failure. (See Table 1)

In terms of the drugs used by the patients, it was discovered that 95 (70.8%) of diabetic patients used at least one oral antidiabetic drug and 83 (61.9%) of diabetic patients used at least one insulin. 48 (12.2%) patients took levothyroxine, 259 (65.9%) took an anticoagulant or at least one antithrombotic drug, and 332 (84.5%) took antihypertensive drugs (ACE inhibitor, ARB, beta blocker, calcium channel blocker, alpha blocker, diuretic) (Table 2).

Levothyroxine was found to be used by 7.5% of men and 15% of women among the patients in the study. Levothyroxine use was found to be statistically significantly higher in women than in men ($p = 0.027$) (Table 2).

Men's mean total cholesterol levels were found to be 180.43 ± 51.2 mg/dl, while women's mean total

Table 1. Evaluation of Chronic Disease Presence in Patients by Gender

		GENDER		Total	*P*
		MEN	WOMEN		
		n (%)	n (%)	n (%)	
Diabetes					
	No	100 (68.0)	159(64.6)	259(65.9)	0.492
	Yes	47(32.0)	87(35.4)	134(34.1)	
Hypertension					
	No	36(24.5)	55(22.4)	91(23.2)	0.628
	Yes	111(75.5)	191(77.6)	302(76.8)	
CKD					
	No	59(40.1)	104(42.3)	163(41.5)	0.677
	Yes	88(59.9)	142(57.7)	230(58.5)	
CHF					
	No	60(40.8)	85(34.6)	145(36.9)	0.213
	Yes	87(59.2)	161(65.4)	248(63.1)	

CKD: Chronic kidney disease, CHF: Congestive heart failure

Table 2. Evaluation of Drug Use in Patients by Gender

		GENDER		Total	*p*
		MEN	WOMEN		
		n (%)	n (%)	n (%)	
Oral antidiabetic drug	Not Using	112(76.2)	186(75.6)	298(75.8)	0.896
	Using	35(23.8)	60(24.4)	95(24.2)	
Insulin	Not Using	123(83.7)	187(76.0)	310(78.9)	0.072
	Using	24(16.3)	59(24.0)	83(21.1)	
Antihypertensive	Not Using Any	21(14.3)	40(16.3)	61(15.5)	0.601
	Using at Least One	126(85.7)	206(83.7)	332(84.5)	
Anticoagulant Antithrombotic	Not Using Any	57(38.8)	77(31.3)	134(34.1)	0.13
	Using at Least One	90(61.2)	169(68.7)	259(65.9)	
Levothyroxine	Not Using	136(92.5)	209(85.0)	345(87.8)	0.027
	Using	11(7.5)	37(15.0)	48(12.2)	

cholesterol levels were found to be 204.2 ± 54.8 mg/dl. Women have higher mean total cholesterol levels than men, and there is a statistical difference ($p = 0$). The mean low-density lipoprotein (LDL) cholesterol levels in all patients were 130.62 ± 43.5 mg/dl, while high-density lipoprotein (HDL) cholesterol levels were 42.90 ± 14.7 mg/dl. Mean LDL levels were found to be 122.1 ± 38.8 mg/dl in men and 135.6 ± 45.5 mg/dl in women. Men's mean HDL levels were found to be 40.4 ± 12.1 mg/dl, while women's levels were 44.3 ± 15.8 mg/dl.Women had higher LDL and HDL levels than men, and the differences were statistically significant ($p = 0.011$ and $p = 0.027$, respectively).

In our study, vitamin D deficiency was defined as a level of less than 20 ng/ml. The mean vitamin D levels in the patients were 15.5 ± 16.0 ng/ml, which was lower than the recommended level. Vitamin D levels in men were found to be 20.3 ± 24.1 ng/ml, while in women they were 13.3 ± 9.83 ng/ml, which is below the optimal value. Men had a higher level of vitamin D than women, and there was a statistical difference ($p = 0.011$). 81.8% of women, 66.6% of men, and 77% of all patients had vitamin D deficiency.

DISCUSSION

There is a scarcity of information on the impact of ageing on HDL composition and function. Early research has discovered that HDL in elderly people has a lower ability to increase cholesterol efflux and inhibit LDL oxidation.6 Total cholesterol and LDL cholesterol levels have been reported to decrease with age in studies conducted in the literature with participants aged 65 and up. Although HDL cholesterol levels do not change with age in cross-sectional studies, it has been reported that it decreases with age in both men and women in most prospective studies.[7,8] When 369 patients aged 70 and up were evaluated as part of the TEKHARF study in our country, metabolic syndrome was found in 59.3% (63.5% of women, 42% of men), with women having a higher rate than men.[9] In our study, dyslipidaemia was found in 51% of men, 57.3% of women, and 54.9% of all patients. The levels of HDL, LDL, and total cholesterol in women were found to be higher than in men. This situation was discovered to be consistent with previous research.

Vitamin D deficiency is common among the elderly and nursing home residents. Reduced ultraviolet light exposure, disorders in the skin's vitamin D synthesis capacity, inadequate dietary vitamin D intake, renal dysfunction, and malabsorption all contribute to an increase in vitamin D deficiency in the elderly.[10] Vitamin D deficiency was found in 47% of women and 36% of men in the multicentre SENECA study, which looked at people aged 71 to 76 in European countries. The prevalence of vitamin D deficiency in people over the age of 50 was found to be 32% in a study of 13432 people in the United States.[11] In a study conducted by Yıldız *et al*. with 213 patients aged 65 and over, the prevalence of vitamin D deficiency was found to be 49.8% (55.2% for females and 37.9% for males) in the Turkish population. Women were found to have significantly higher levels of vitamin D deficiency than

Table 3. Comparison of Hemogram and Biochemistry Values by Gender

	MEN		WOMEN		TOTAL		*p*
	n	Median ± std	n	Median ± std	n	Median ± std	
WBC	147	12.4 ± 8.72	246	9.1 ± 4.76	393	10.3 ± 20.9	0.126
HB	147	10.8 ± 2.57	245	10.58 ± 2.29	392	10.6 ± 2.40	0.257
HTC	147	33.8 ± 6.88	246	33.2 ± 7.90	393	33.5 ± 7.53	0.433
MCV	147	87.4 ± 11.1	246	86.9 ± 8.36	393	87.1 ± 9.49	0.662
Glucose	147	125.9 ± 53.9	245	131.4 ± 64.8	392	129.3 ± 60.9	0.385
Urea	147	82.2 ± 56.9	245	72.7 ± 50.2	392	76.2 ± 53.0	0.086
Creatine	147	1.7 ± 1.13	245	1.6 ± 3.83	392	1.6 ± 3.11	0.793
eGFR	147	50.08 ± 25.4	245	50.6 ± 24.5	392	50.4 ± 24.8	0.836
Sodium	146	138.6 ± 6.49	245	137.7 ± 7.42	391	138.0 ± 97.09	0.252
Potassium	146	4.4 ± 0.78	245	4.2 ± 0.76	391	4.28 ± 0.74	0.088
Calcium	145	8.56 ± 0.90	245	8.9 ± 5.15	390	8.8 ± 4.12	0.320
ALT	143	29.18 ± 23.5	244	27.7 ± 26.3	387	28.2 ± 7.25	0.876
AST	143	39.30 ± 29.1	243	35.9 ± 70.2	386	37.1 ± 6.20	0.741
Iron	100	60.5 ± 43.3	162	55.0 ± 40.7	262	57.1 ± 41.8	0.301
TIBC	99	214.3 ± 87.0	160	225.5 ± 90.9	259	221.2 ± 89.5	0.327
Ferritin	96	188.93 ± 58.9	156	145.51 ± 63.8	252	162.1 ± 89.5	0.095
Total protein	142	6.4 ± 0.9	242	6.3 ± 0.8	384	6.37 ± 0.87	0.438
Albumin	142	3.60 ± 4.38	242	3.35 ± 1.21	384	3.4 ± 2.83	0.391
Total cholesterol	123	180.43 ± 51.2	203	204.2 ± 54.8	326	195.2 ± 54.6	0.000
Triglyceride	122	122.6 ± 105.4	202	138.6 ± 77.5	324	132.6 ± 89.2	0.119
LDL	107	122.1 ± 38.8	180	135.6 ± 45.5	287	130.6 ± 43.5	0.011
HDL	108	40.4 ± 12.1	181	44.3 ± 15.8	289	42.9 ± 14.7	0.027
TSH	121	1.09 ± 1.10	204	1.26 ± 1.22	325	1.19±1.81	0.209
Vitamin B12	100	436.8 ± 309.3	170	465.9 ± 456.9	270	455.1 ± 408.1	0.572
Vitamin D	51	20.3 ± 24.1	110	13.3 ± 9.83	161	15.5 ± 16.0	0.011

WBC: White blood cell count HB: Hemoglobin, HTC: Hematocrit, MCV: Mean corpuscular volume, eGFR: Estimated glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TIBC: Transferrin and iron-binding capacity, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoproteins, TSH: Thyroid-stimulating hormone

men.[12] Total vitamin D deficiency was found to be 33.4% in 225 elderly people living in nursing homes and 195 elderly people living in their own homes in a study by Atlı *et al*.[13] Vitamin D deficiency was found in 77% of the people in our study (81.8% in women and 66.6% in men), with women having more vitamin D deficiency. In our study, 7.8% of male patients, 6.3% of female patients, and 6.8% of all patients had vitamin D levels that were within the recommended range (> 30 ng/dl). In our study, the elderly had a higher prevalence of vitamin D deficiency than the rest of the population. Women had higher levels of vitamin D deficiency, which is consistent with previous research.

CONCLUSION

According to the findings of this study, in which the health status of super-elderly people followed and treated in Internal Medicine clinics were evaluated internally, women have higher total cholesterol, LDL, and HDL levels than men, and there is a significant difference between the two genders. Men have higher mean vitamin D levels than women. Vitamin D deficiency was found to be high in both genders. The goal of this study is to raise awareness about low vitamin D levels, which may be linked to increased fragility, especially in the elderly, and to encourage researchers to

investigate the causes and emphasise the importance of supplementation. These laboratory tests should be controlled in this age group.

Authors' Contribution

Study Conception: EY, TA,; Study Design: EY, TA,; Supervision: TA,; Materials: EY,; Data Collection and/or Processing: EY,; Statistical Analysis and/or Data Interpretation: EY, TA,; Literature Review: EY,; Manuscript Preparation: EY, TA and Critical Review: EY, TA.

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Original Article

pediatrics & General Surgery

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Retrospective analysis of cases with tuberculous meningitis: single center experience

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ABSTRACT

Objectives: A total of 172 patients were retrospectively investigated who were admitted to the Pediatric Department of Dicle University School of Medicine with the diagnosis of tuberculous meningitis. Demographic data, clinical, laboratory and radiological findings and responses to treatment were analyzed. Of all patients 124 (72.1%) were under 5 years of age and 109 were males. The most common symptoms on admission were fever (%71), vomiting (60%), convulsion (38%), and headache (31%). Forty-seven (23.8%) patients had positive family history of tuberculosis. Tuberculin skin test positivity was seen in 19.6% and 20.1% had positive BCG scar. Of all patients 32 (18.6%) were in stage I, 82 (47.7%) were in stage II and 58 (33.7%) were in stage III on admission. Chest X-Ray showed pathological findings in 60.9% of all patients. Hydrocephalus was detected in 149 patients on cranial tomography. Ventriculo-peritoneal shunt was performed in 79 patients with hydrocephalus. Totally, 24 deaths were detected from all patient records.

Since the diagnosis of tuberculous meningitis is difficult and the disease has a high morbidity and mortality rate, the importance of preventive measures in the control of the disease has been emphasized in this study

Keywords: children, tuberculosis, meningitis

Tuberculosis (TB), one of the oldest diseases in history, continues to be one of the most common infectious diseases in the world and constitutes an important health problem especially in developing countries, including our country. Today, more than 40% of the world's population is infected with tuberculosis bacillus, and 1-3 million new tuberculosis cases are reported each year in children younger than 15 years of age. It has been reported that the majority of these cases are located in developing countries with poor living conditions. [1] In our country, the prevalence of infection was found to be 25% (11,578,000 people), and the prevalence of the disease was 0.36% per thousand, which was last done in 1982. In addition, as seen in this study, the prevalence of tuberculosis is high in our region (0.74%), and as a result, tuberculous meningitis (TBM) is frequently encountered. [2]

Although the definitive diagnosis of tuberculous meningitis is made by direct smear from CSF(Cerebrospinal fluid) or the demonstration of Mycobacterium tuberculosis (M. Tbc) by culture, the diagnosis can still be made by clinical, demographic, radiological, and contact anamnesis since it takes time and is rarely positive.

Tuberculous meningitis occurs in 0.3% of children with untreated primary infection.[3] It is an infection with high morbidity and mortality in childhood. Tuberculous meningitis is the most common form of central nervous system tuberculosis.[4] Tuberculous

Received: *December 23, 2021****; Accepted:*** *January 11, 2022****; Published Online:*** *January 29, 2022*

How to cite this article: *Demir Yiğit Y, Yiğit E. Retrospective analysis of cases with tuberculous meningitis: single center experience. DAHUDER M J 2022, 2(1):16-23.*

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meningitis is very rare in children younger than four months because the pathological process is completed in such a short time. It is most common in children between the ages of 6 months and 4 years (first five years). At this age, it usually develops within the first 2-6 months of primary infection.[4-6]

In current study, clinical, laboratory, radiological findings and responses to treatment of 172 patients with tuberculous meningitis who were followed up in our clinic were evaluated retrospectively, and the results were evaluated in the light of today's literature.

METHODS

In this study, 172 patients were hospitalized and treated with the diagnosis of tuberculous meningitis in the Infectious Diseases Clinic of the Department of Pediatrics of the Dicle University, and then followed up in the control outpatient clinic were included.

The study was done retrospectively. General information from the follow-up cards of the patients; age, gender, residence address, application complaints, BCG (Bacillus Calmette-Guerin vaccine), PPD (Pürified Protein Derivative Test), which period they applied, family histories, PA lung grammar, cranial CT (Computed Tomography) and MRI (Manyetik rezonans) results, CSF results, blood biochemistry (ALT, AST, urea, creatinine) were recorded and the existing results were evaluated.

Diagnosis of tuberculous meningitis was based on the history, physical examination, laboratory findings, microbiological and biochemical examination findings of Cerebrospinal fluid (CSF), and radiological findings. Among these, the appearance of ARB (Acid resistant bacilli) in the "Ehrlich-ZiehlNeelsen (EZN)" staining of CSF and/or the production of Mycobacterium tuberculosis in Löwenstein-Jensen medium; Findings of more than 10 cells per mm^3 with signs of subacute meningitis (signs of meningeal irritation lasting longer than four days), biochemical features of CSF (high protein, low sugar, and chloride); M. tuberculosis growth in another anatomical region or detection of ARB in a direct stained preparation were considered as the main determinants for the diagnosis of the disease.[7]

In all patients diagnosed with TB, standard 4 antituberculous therapy (2 months INH + RIF + PZA + SM or EMB, 10 months INH + RIF) and additional methylprednisone (1-2 mg/kg/day) for the first 4-6 weeks or dexamethasone (0.5-1 mg/kg/day) and if necessary, acetazolamide (40 mg/kg/day) treatment was administered.

Descriptive statistics for continuous variables were expressed as mean, standard deviation, minimum and maximum values, while categorical variables were expressed as numbers and percentages. Chi-square test was used to determine the relationship between groups and categorical variables, and Student-t test was used to compare group means of continuous vari-

Table 1. General information about the patients

Age(years)	n	Percent
< 5 years old	124	72.1
> 5 years old	48	27.9
Gender		
Male	109	63.4
Female	63	36.6
BCG		
Positive	30	20.1
Negative	119	79.9
PPD		
Negative	115	80.4
Positive	28	19.6
Family history		
Negative	47	23.3
Positive	125	72.7

BCG: Bacillus Calmette-Guerin vaccine, PPD: Purified Protein Derivative Test

ables. Statistical significance level was accepted as $p < 0.05$ by using the "SPSS for Windows" statistical package program in the calculations.

RESULTS

172 patients who were clinically diagnosed with tuberculous meningitis were included in the study. The mean age of the patients was 59.7 ± 45.6 months (4 months-15 years). The mean age of 124 (72.1%) patients was 5 years or less, and 48 (27.9%) patients were older than 5 years (Table 1). Of the patients, 63 (36.6%) were female and 109 (63.4%) were male. The male/female ratio was found to be 1.74 (Table 1).

Patients applied mostly in June (22.1%). (Fig. 1)

In the records of the patients, 149 patients have BCG scars. Of these, 119 (79.9%) had negative BCG and 30 had positive BCG (Table 1). One-hundred and forty-three of our patients had PPD results. PPD test results were negative in 115 (80.4%) of 143 patients, and positive in 28 (19.6%) patients. (Table 1)

While there was family history in 125 (72.7%) of our patients included in the study, there was no family history in the 47 (27.3%) patients (Table 1). BCG positivity was found to be %18.3 in those with a positive family history. When the clinical period of the patients was examined at the time of hospitalization; it was seen that 32 (18.6%) of the patients came in stage I, 82 (47.7%) in stage II, 58 (33.7%) in stage III.

Fever was among the most common symptoms in 122 (71%) of our patients at the time of admission to the clinic. (Table 2).

Pathological chest X-ray findings were found in 56 (60.9%) of 92 patients whose chest X-ray findings were recorded. Of these, 27 (15.7%) parenchymal infiltration, 15 (8.7%) miliary appearance, 9 (5.2%) hilar LAP, [3 (1.7%) unilateral, 6 (3.5%) bilateral LAP], 2 (1.2%) atelectasis, 1 (0.6%) pleural effusion, 1 (0.6%) empyema, 1 (0.6%) LAP + consolidation. 36 (39.1%) chest X-ray of the patient was normal.

Pathological cranial CT imaging results were found in 157 of 172 patients. The most common complication was hydrocephalus, and 79 (45.9%) of these patients underwent ventriculoperitoneal shunt operation (Table 3).

CSF glucose levels were below 10 mg/dL in 15 (8.7%) of the patients, between 11-40 mg/dL in 99 (57.6%), and between 41-80 in 51 (29.7%) patients. Seven (4.1%) were found to be over 80. CSF glucose was below 10 mg/dL in five patients, CSF glucose was between 11-40 mg/dL in 11 patients, and CSF glucose was between 41-80 mg/dL in 8 patients.

When the CSF protein was biochemically examined, it was found that 44 (32.9%) of the patients were between 0-50 mg/dL, 19 (14.1%) of them were between 51-100 mg/dL, 53 (39.6%) of them were between 101-200 mg/dL, 13 (9.7%) were between 201-500 mg/dL and 5 (3.7%) of them were over 500 mg/dL.

Lymphocyte dominance was observed in 143 (83.1%) of the admitted patients, while PNL was dominant in CSF in 29 (16.9%). When the number of cells in the CSF was examined, 7 (4%) of the patients were between 0-10/mm^3, 55 (32%) of them were between 11-100/mm3, and 84 (48.8%) of them were between 101-500/mm^3. and in 26 (15.2%) of them were found to be above 500/mm^3. The presence of M.Tuberculosis was demonstrated in CSF by PCR (Polymerase Chain Reaction) in 3 patients.

The white blood cell (WBC) count of the patients whose hemogram results were examined was < 4000/

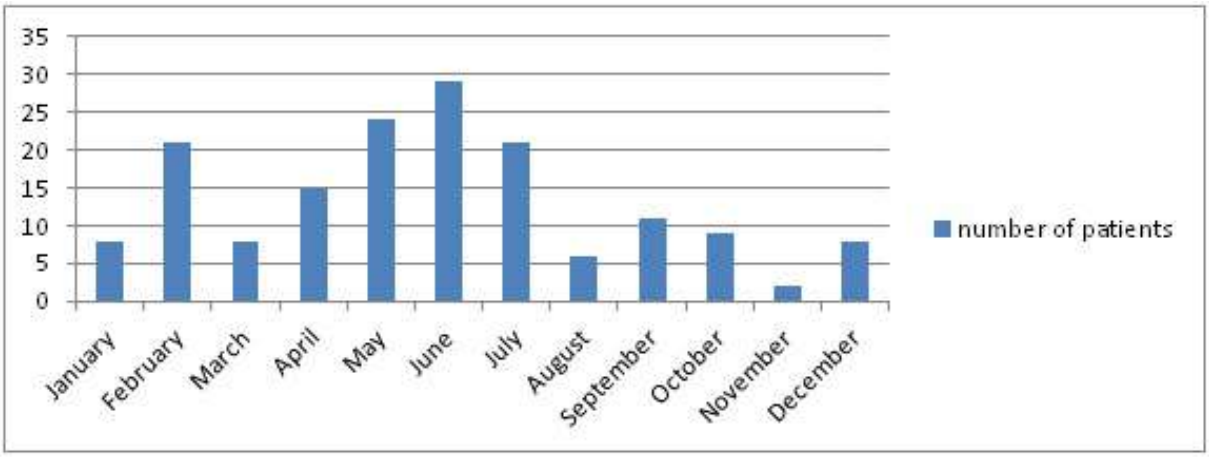

Fig. 1. Distribution of the number of patients according to the seasons

Table 2. Symptoms of the patients at the time of first admission

Symptoms	n	%
Fever	122	71
Vomiting	104	60
Epilepsy	66	38
Headache	54	31
Diarrhea	28	16
Confusion	24	14
Cough	16	9
Neurological deficit	14	8
Nausea	13	8
Abdominal pain	13	8
Dyspnea	9	6
Anorexia	5	3
Weakening	4	2
Sweating	3	2
Weakness	3	2
Not sucking	2	1
Abdominal swelling	1	1

mm3 in 3 (1.7%) and between 4000-10000/mm3 in 66 (38.4%) and > 10000/mm^3 in 103 patients. WBC mean of the patients was found as 14100/mm^3. As a result, the majority of the patients presented with leukocytosis.

When the mean AST, ALT, urea, and creatinine values of the patients whose biochemistry results were examined, it was seen that they applied with mild AST elevation. The number of patients with AST values above normal was 75. ALT, urea, and creatinine values were found to be normal.

Hydrocephalus was detected in 172 patients 149 of them who were examined retrospectively, and shunt operation was performed in 79 (45.9%) of these patients.

Toxicity was detected in 12 (7%) of the 172 patients examined. Drug toxicity was accepted as a more than a 3-fold increase in AST, ALT levels, increase in bilirubin levels, jaundice, nausea, and vomiting. medications were discontinued. In these patients, re-treatment was continued after the AST and ALT levels of the drugs returned to normal. Of 172 patients, 24

Table 3. Cranial CT results of the patients

CT findings	n	%
Hydrocephalus	149	94.9
Meningeal/parenchymal involvement	49	31.2
Subdural effusion	16	10.2
Cerebral atrophy	12	7.6
Tuberculoma	12	7.6
Cerebral infarction/embolism	11	7.0
Brain edema	7	4.5
Hematoma	3	1.9
Ischemia	2	1.3
Normal	12	7.6

(%14) died. On average, the hospital stay of the patients was 23.5 ± 14.5 days.

Of the cases that resulted in death, 19 (79.1%) were within the first 5 years of age, and 5 (20.9%) were above 5 years of age. Of the deceased patients, 3 (12.5%) were in stage I, 12 (50%) were in stage II, and 9 (37.5%) were in stage III.

DISCUSSION

Tuberculous meningitis, which is the most serious complication of tuberculosis in childhood and the most common cause of death from tuberculosis, is most common in children aged 6 months to 4 years, accounting for approximately 10% of tuberculosis cases. In our study, the ages of our patients were found to be between 4 months and 15 years. The mean age of 124 (72.1%) patients was 5 years or less, and 48 (27.9%) patients were older than 5 years (Table 1). Of the 172 cases in our study, 63 (36.6%) were female and 109 (63.4%) were male. The male/female ratio was found to be 1.74 (Table 1). The mean age of our patients was 59.7 ± 45.6 months.

Recent studies on the BCG vaccine show that the protective effect of the BCG vaccine is 50% against pulmonary tuberculosis in children and adults, and 50-80% against tuberculous meningitis and other disseminated tuberculosis types.[6, 8-11] It is widely believed that the main effect of the vaccine prevents the development of life-threatening forms such as miliary and central nervous system tuberculosis. A dose between 0-3 months in endemic populations as the age of vaccination is a second dose to be given at the beginning of school. Considering the results of our patients' vaccination with BCG vaccine, the low vaccination rate of 20.1% shows the importance of maintaining BCG vaccination for our region in preventing disease with serious morbidity and mortality, such as tuberculosis and, more importantly, tuberculous meningitis, one of the disseminated forms of tuberculosis. It can be thought that this low vaccination rate is due to social, cultural, and traditional reasons, lack of education, the inadequacy of health services, the problem of access to services, effectiveness of vaccination, inadequacy of basic and preventive health services.

In various studies, the rate of having a person with tuberculosis in the family or in the immediate environment was found to be 30-80%. The recent diagnosis of tuberculosis in 47 (27.3%) of our patients from family members or close relatives is consistent with previous studies. Despite these family histories, it was observed that most of our patients did not have family screening. Therefore, it was concluded that the deficiencies in the reporting of the disease with such serious consequences and in family screening should be reviewed. Screening the family members of adults with active tuberculosis and administering antibiotic prophylaxis to children under 5 years of age and other PPD positive individuals are of vital importance in preventing the spread of the disease.[6, 12]

PPD test maintains its importance in diagnosing tuberculosis. it has been reported in various sources that 50% of patients with tuberculous meningitis may have a positive PPD test.[6, 10, 11, 13] It may be negative in miliary spread, immunosuppression, viral infections, especially in infants and young children. In some cases, it may be positive after starting tuberculosis treatment. In tuberculous meningitis, both PPD and pulmonary findings may be negative. In our study, 115 (80.4%) of our patients had negative PPD results and 28 (19.6%) had positive PPD results. In their study consisting of 214 patients, Yaramış *et al*. found PPD positive in 64 (30%) patients.14 Nguyen *et al*. stated that PPD may be negative at a rate of 50-70% in patients.15 In previous studies, the tuberculin test performed with 100 U PPD in patients with tuberculous meningitis was found to be 20% negative.16 The PPD solution applied in our study was 5 U tuberculin test solution. In recent studies, the tuberculin test performed with 10-100 U PPD has been shown to be 75% positive.17

TB meningitis is the most serious form of tuberculosis, usually fatal if left untreated. Symptoms are similar to other forms of meningitis, with an onset that lasts days or weeks. It is clear that early diagnosis and treatment have a significant impact on mortality and morbidity. atypical onset; It may also be in the form of bronchopneumonia, findings suggestive of intracranial mass, GIS symptoms, typhoid or epilepsy. Therefore, the possibility of TBM should be considered in patients presenting with these tables. In their study consisting of 497 male and 360 female cases, Girgis *et al*. reported fever in 90% of the cases, headache in 63%, vomiting in 49%, and lethargy in 32%.18 In their study consisting of 214 cases, Yaramış *et al* found fever in 91%, vomiting in 87%, altered consciousness in 63%, seizures in 62%, and headache in 58%.14

Studies have reported that patients present with nonspecific symptoms such as restlessness, weakness, fever, fatigue, and headache.[19-21] Fever was the most common in 71% of the patients, vomiting in 60%, convulsions in 38%, headache in 31%, diarrhea in

16%, confusion in 14%, cough in 69%, cough in 8%. Neurological deficit, nausea and abdominal pain were the most common symptoms. When compared with the literature data, symptoms were found to be similar.

Diagnosis of tuberculous meningitis is still a problem, although the disease may start acutely in 50% of infants, it can be subacute in children and adults. History and laboratory tests are often nonspecific and rarely pathognomonic. Therefore, radiological imaging, especially cranial imaging, is of great importance in the early diagnosis and treatment of tuberculous meningitis, which has serious morbidity and mortality consequences.

In patients with suspected tuberculous meningitis, showing hydrocephalus, infarction, tuberculoma, edema, ventricular dilatation, involvement of the meninges and especially the basilar region, which may vary according to the degree of cranial CT disease, is important for diagnosis. Hydrocephalus is the most common complication seen in tuberculous meningitis and occurs in the acute period with obstruction of the basal systems and is usually of the communicative type.4 It is reported that the most frequently reported data in cranial CT is hydrocephalus, and it constitutes a greater majority in children than in adults.

In our study, cranial CT results of 157 patients were evaluated retrospectively, 149 (94.9%) of patients had hydrocephalus, 49 (31.2%) had meningeal/parenchymal involvement. and 12 (7.6%) patients had normal results. Hydrocephalus was the most common complication.

Doer *et al*. In their study of 31 tuberculous meningitis patients aged between 3 months and 15 years, had at least one cranial imaging performed in all of the patients. They found abnormalities in 26 (87%) of the patients. They detected hydrocephalus in 17 (57%) patients, meningeal involvement in 12 (40%) patients, tuberculoma in 8 (27%) patients, cerebral infarction in 3 (10%) patients, and multiple abnormal findings in some patients. They found normal imaging in four patients. [22]

In tuberculous meningitis, cranial tomography is useful in monitoring the disease, early diagnosis and treatment of complications, and determining the prognosis as well as in the diagnosis 23. It has been shown that there is a relationship between the symptoms of the disease in terms of onset, prognosis, and sequelae. [20]

Tuberculous meningitis usually has an insidious and chronic onset, so diagnosis can be difficult, mostly in stage II. or III. diagnosis is made. When examining the period in which the 172 cases included in the study came; it is seen that 32 (18.6%) of the patients came to stage I, 82 (47.7%) to stage II, 58 (33.7%) to stage III. Girgis *et al*. reported that 4% of patients were in stage I, 34% were in stage II, and 62% were in stage III. [18]

Chest radiography findings were recorded in 92 of 172 patients included in the study. Pathological chest radiography findings were found in 56 (60.9%) of 92 patients. Of these, 27 (15.7%) parenchymal infiltration, 15 (8.7%) miliary appearance, 9 (5.2%) hilar LAP (3 (17%) unilateral, 6 There were bilateral (3.5%) bilateral LAP), 2 (12%) atelectasis, 1 (0.6%) pleural effusion, and 1 (0.6%) LAP + consolidation. Chest X-ray of 36 (39.1%) patients was normal. Girgis *et al*. showed that lung grammar was normal in 169 (40%) of 423 cases. In the same study, perihilar nodular infiltration in the lung grammar of 125 (29.5%) patients, lower lobe infiltration in 50 (11.8%), upper lobe infiltration in 40 (9.4%) and 9 (2%) patients. They determined that there is miliary involvement.18

It was determined that 51% of the patients resided in city centers and 49% resided in districts or villages. In their study, Yaramış *et al*. showed that 14% of the patients came from the city centers, 34% from the districts, and 52% from the villages.14 CSF of our cases was evaluated in terms of protein, glucose, and white blood cell. The presence of M Tuberculosis was demonstrated by PCR in the CSF of 3 patients. CSF glucose levels were below 10 mg/dL in 15 (8.7%) patients, between 11-40 mg/dL in 99 (57.6%), 41-80 mg/dL in 51 (29.7%) patients. 7 (4.1%) were found to be above 80 mg/dL. When the CSF protein of the patients was biochemically examined, it was between 0-50 mg/dL in 44 (32.9%) patients, between 51-100 mg/dL in 19 (14.1%) and 101-200 in 53 (39.6%) patients. It was found to be between mg/dl, 201-500 mg/dL in 13 (9.7%) and over 500 mg/dL in 5 (3.7%) patients.

Lymphocyte dominance was observed in 143 (83.1%) patients, while PNL dominance was observed in CSF in 29 (6.9%). The number of cells in CSF of these patients was between 0-10/mm3 in 7 (4%) patients, between 11-100/mm3 in 55 (32%) and 101-500/mm3 in 84 (48.8%) patients and 500/mm3 and above were found to in the 26 (15.2%) patients.

Girgis *et al*. investigated CSF glucose, protein amount, and leukocyte count in cases with tuberculous meningitis. In their study, they found the average CSF glucose 22 ± 15 mg/dL, CSF protein 220 ± 20 mg/dL, and CSF leukocyte count 437 ± 347/mm3. [18]

In their study, Yaramış *et al*. found CSF glucose

below 10 mg/dL in 12% of the cases, between 10-40 mg/dL in 71% and between 40-80 mg/dL in 17%. They found CSF protein below 100 mg/dL in 23% of the patients, between 100-200 mg/dL in 62% and over 200 mg/dL in 15%.14 In the same study, the CSF leukocyte count was below 500 /mm^3 in 85% of the cases and over 500/mm^3 in 15%. And they stated that 83% of the leukocytes seen in CSF are lymphocytes and 17% are fragmented. In the CSF examination, which is the most important laboratory test, it has been reported that the leukocyte count varies between 500/mm^3 (compartmental lymphocyte dominance in the early period, lymphocyte dominance in the early period), the glucose level is low in the early period or is always low in the normal late period, and the protein level is usually high. [24] The mean white blood cell count was found to be 13.325/mm^3. Girgis et al found the mean peripheral white blood cell count of cases with tuberculous meningitis to be 11.600/mm^3. When compared with the literature data, it was seen that the patients with tuberculous meningitis who had similar leukocyte counts presented with mild leukocytosis. [19] While other laboratory results (urea, creatine, and transaminase elevation) were found to be high in approximately 20% of patients by Girgis colleagues, they were found to be high only in 10 patients who were evaluated as toxicity by Yaramış et al. [14,18]

CONCLUSION

TBM should be detected in the early period and their contagious feature should be eliminated, and uninfected people should be vaccinated. People with a high risk of infection should be protected from the disease by giving preventive antituberculosis drugs, and society and families should be educated and sensitized about the disease.

Authors' Contribution

Study Conception: YDY,; Study Design: YDY,; Supervision: YDY,; Materials: YDY,; Data Collection and/or Processing: YDY,; Funding: EY,; Statistical Analysis and/or Data Interpretation: YDY,; Literature Review: YDY,; Manuscript Preparation: YDY and Critical Review: YDY.

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Case Report

Internal Medicine

DAHUDER Medical Journal
e-ISSN: 2791-9250

A Case of Autoimmune Hepatitis Presenting with Fever and Bicytopenia

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ABSTRACT

Objectives: Autoimmune hepatitis is a chronic inflammatory liver disease of unknown cause. In the etiology, genetic predisposition and triggering factors such as viruses (hepatitis A, hepatitis B, hepatitis C, Ebstein Bar virus, cytomegalovirus), bacteria, drugs (propylthiouracil, nitrofurantoin, isoniazid, etc.) are emphasized. Cases may be asymptomatic or present with complaints such as fatigue, weakness, jaundice, upper abdominal discomfort, pruritis, loss of appetite, nausea and fever. We presented a case of autoimmune hepatitis presenting with fever and bicytopenia.

Keywords: Autoimmune hepatitis, fever, bicytopenia

Autoimmune hepatitis (AIH) is a progressive, chronic necroinflammatory liver disease of unknown etiology.[1] Considering the etiopathogenesis of AIH; It is emphasized that genetic predisposition causes impaired self-tolerance to liver autoantigens and that both direct cell-mediated and antibody-mediated cell damage develop in these susceptible individuals with the effect of triggering factors. Although it varies according to ethnic origins, in terms of genetic predisposition, HLA DR3, HLA DR4, DR7, HLAB1 alleles are prominent.[2] AIH is more common in women and its prevalence varies widely between geographic regions.[3, 4] Patients may present with a wide variety of symptoms such as fatigue, weakness, jaundice, upper abdominal pain, pruritus, anorexia, nausea, and fever, which makes differential diagnosis necessary with many diseases. For the diagnosis of the disease after exclusion; determined by the international autoimmune hepatitis study group, female gender, the ratio of alkaline phosphatase elevation to aminotransferase elevation, total globulin, gamma globulin or IgG elevation, autoantibodies (ANA, ASMA or Anti-LKM), hepatitis virus indicators, hepatotoxic drug use, alcohol, liver histology, the presence of other autoimmune diseases in the patient or first degree relatives and some optional additional factors are used in the scoring system. (Table 1).[5] İn this study, we explained a case of autoimmune hepatitis presenting with fever and bicytopenia.

CASE

A 39-year-old male patient was admitted to our emergency department with complaints of fever and malaise. It was learned that the patient's complaint of fever continued intermittently for 2 days, and 39 C was found in the measurements. There was no feature in the patient's history. He also had no history of alcohol or smoking use. On physical examination; His general condition was good, he was conscious, cooperative and oriented. His blood pressure was 120/80

Received: *December 31, 2021****; Accepted:*** *January 8, 2022****; Published Online:*** *January 29, 2022*

How to cite this article: *Oral A, Türker F, A Case of Autoimmune Hepatitis Presenting with Fever and Bicytopenia. DAHUDER M J 2022, 2(1):24-27.*

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Available at http://dergipark.org.tr/en/pub/dahudermj

Table 1. Diagnostic criteria of the Autoimmune Hepatitis

Clinical feature	Score
Female gender	+2
ALP: AST ratio	
< 1.5	+2
1.5 – 3.0	0
> 3.0	-2
Serum globulin or IgG above normal	
> 2.0	+3
1.5 – 2.0	+2
1.0 – 1.5	+1
< 1.0	0
ANA, SMA, LKM1	
> 1:80	+3
1:80	+2
1:40	+1
< 1:40	0
Illıcit drug use history	
Positive	-4
Negative	+1
Average alcohol intake daily	
< 25 g/ day	+2
> 60 g/ day	-2
Histologic findings	
Interface hepatitis	+3
Lymphoplasmacytic infiltrate	+1
Rosette formation	+1
None of the above	-5
Biliary changes	-3
Other changes	+2
Other autoimmune disease	+2
AMA positivity	-4
Hepatitis viral markers	
Positive	-3
Negative	+3
Aggregate score without treatment	
Definite AIH	> 15
Probable AIH	10-15

ALP = alkaline phopshatase; AST = aspartate aminotransferase; IG = İmmunoglobulin; ANA = antinuclear antibody; SMA = smooth muscle antibody; LKM1 = Lİver kidney microsomal antibody; AMA = antimitochondrial antibody.

mmHg, heart rate was 78/min, and fever was 39 C. In the abdominal examination, hepatomegaly with a rib arc exceeding 3 cm was detected. No abdominal tenderness, rebound and defense were detected. Blood count, C-reactive protein (CRP), complete urinalysis, and entire abdominal ultrasonography were requested from the patient. As a result of the examinations; the patient who was found to have leukopenia, thrombocytopenia and hepatosplenomegaly was admitted to the ward for differential diagnosis. In the examinations made during the patient's admission to our clinic are shown in Table 2. Due to fever and high CRP, the patient was consulted to infectious diseases department. Viral markers, blood culture, Rose Bengal and Wright tests were sent from the patient and ceftriaxone 2 g/day treatment was started. In the follow-ups, the patient had a decrease in fever, an increase in the leukocyte and thrombocyte counts, and an improvement in the CRP value. However, the patient's AST, ALT, ALP, GGT values increased compared to the baseline. In the patient's examinations, HBsAg (-), anti-HIV, anti-HCV, Epstein-Barr virus (EBV), parvovirus B 19, influenza A/B, cytomegalovirus (CMV), brucella agglutination (Wright) and Rose Bengal tests were found to be negative. The patient was evaluated in the hematology department with the result of peripheral blood smear and no pathology was observed. While the fever did not recur, the CRP level decreased to normal levels. Antibiotic treatment was stopped on the fifth day of hospitalization. The patient was consulted to the gastroenterology department because of the gradual increase in liver enzymes.

For the etiology, tests were requested from the patient. As a result of the examinations; total protein level: 6.0 g/dl (6.40-8.30 g/dl), albumin level: 3.6 (3.5-5.20), antinuclear antibody (ANA) (-), antismooth muscle antibody (ASMA) (-), antimitochondrial antibody (AMA) (-), liver/kidney microsomal autoantibody-1 (anti-LKM-1) (-) was determined as. The patient was diagnosed with autoimmune hepatitis using the scoring system determined by the International Autoimmune Hepatitis Study Group (ALP/AST: 2 points, viral markers: 3 points, alcohol: 2 points, hepatotoxic drug: 4 points; total: 11 points so Probable AIH). On the 7th day of the patient's treatment, whose steroid treatment was started by the gastroenterology department, his clinic improved and the patient's ALT/AST level was found to be 62/74 U/L. The patient was discharged to follow up outpatient clinic with current treatment.

DISCUSSION

Autoimmune hepatitis is a chronic liver disease in which genetic predisposition and triggering environmental factors play a role in its etiology.[1] While the cases in autoimmune hepatitis may be asymptomatic, they may present with acute hepatitis, fulminant liver failure, subfulminant liver failure, chronic hepatitis and liver cirrhosis.6 Patients may present with

Table 2. Patients Laboratory

Hemoglobin	12.2 g/dL (14-17.5)
Leukocyte count	2640/mm3 (4400-11.300/)
Platelet count	91.000/mm3 (150.000-400.000)
Aspartate aminotransferase (AST)	82 U/ L (5-34)
Alanine aminotransferase (ALT)	182 U/L (0-55)
Lactate dehydrogenase (LDH)	414 U/L (125-220)
Blood urea nitrogen (BUN)	15 mg/dL (8.9-20.6)
Creatinine	0.85 mg/dL (0.72-1.25)
Sodium	135 mEq/L (136-145)
Potassium	4.0 mg/dl (3.10-5.10)
C-reactive protein (CRP)	21.1 mg/L (<5)
INR	0.90 (0.75-1.0)
Total bilirubin	0.7 mg/dL (0.31-1.20)
Direct bilirubin	0.2 mg/dL (<0.50)
Gammaglutamyl transferase (GGT)	81 U/L (11-50)
Alkaline phosphatase (ALP)	67 U/L (40-150)

nonspecific complaints such as fatigue, nausea, itching, abdominal pain, loss of appetite and fever, and findings such as jaundice, hepatomegaly, and splenomegaly may be detected in their physical examination.[7] On the other hand, laboratory tests are used because they contribute both to the diagnosis of the disease and to the differential diagnosis of similar conditions. For this purpose, frequently used examinations; complete blood count, total bilirubin, GGT, ALP, AST, ALT, prothrombin time and autoantibodies (AMA, ASMA, Anti LKM-1, ANA).[8] In addition to hematological disorders such as thrombocytopenia, leukopenia, and anemia, an increase in CRP and elevated serum aminotransferases at different levels can be detected in AIH. GGT and ALP levels are usually normal or slightly elevated.[3, 9] In this case; There was a finding of hepatosplenomegaly accompanying complaints such as fever and malaise, and in the first examinations, ALT, AST elevation and bicytopenia were detected. With these results, HBsAg, anti-HIV, anti-HCV, Epstein-Barr virus (EBV), parvovirus B 19, influenza A/B, cytomegalovirus (CMV blood culture, rose bengal and Wright tests were sent from the patient for differential diagnosis of infection). On the other hand, due to fever and bicytopenia, the patient was evaluated for hematological malignancies in the differential diagnosis. As a result, these diagnoses were excluded, since no findings in favor of malignancy and infection were found in the examinations performed. In the diagnosis of autoimmune hepatitis, a scoring system based on the criteria determined and reviewed by the "International Autoimmune Hepatitis Study Group" is used.[5, 10, 11] As a result of this scoring system, cases can be defined as definite or probable AIH. We scored our case according to these criteria and diagnosed autoimmune hepatitis. Corticosteroids can be used as monotherapy or in combination with azathioprine for the initial treatment of patients diagnosed with autoimmune hepatitis. Especially the patients who are diagnosed early respond well to these treatments. On the other hand, cyclosporine A, tacrolimus, cyclophosphamide, mercaptopurine, mycophenolate mofetil and ursodeoxycholic acid are other agents that can be used in the treatment.[12, 13, 14] In our case, after the diagnosis was made, corticosteroid treatment was started in the gastroenterology department, and laboratory values decreased significantly in the follow-up. Consequently; Since early diagnosis and treatment of autoimmune hepatitis in patients presenting with fever and bicytopenia have significant effects on progression, it must be considered.

Authors' Contribution

Study Conception: AO, FT,; Study Design: AO, FT,; Supervision: AO, FT,; Materials: AO, FT,; Data Collection and/or Processing: AO, FT,; Statistical Analysis and/or Data Interpretation: AO, FT,; Literature Review: AO, FT,; Manuscript Preparation: AO, FT and Critical Review: AO, FT.

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Case Report

Internal Medicine

DAHUDER Medical Journal
e-ISSN: 2791-9250

Etanercept-induced thrombocytopenia in a patient with ankylosing spondylitis

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ABSTRACT

Objectives: Tumor necrosis factor alpha (TNF-α), which is produced by macrophages and activated T lymphocyte cells, plays a main role in inducing further stimulation of other inflammatory cells. Anti-TNF-α drugs are used for induction and preservation of remission in patients with Ankylosing spondylitis. Etanercept, it is possible that the use of its inhibitors may cause cytopeniabut isolated thrombocytopenia is an uncommon adverse event. We report the case of a 40-year-old man diagnosed with Ankylosing spondylitis who developed Etanercept-induced isolated thrombocytopenia.

Keywords: Thrombocytopenia, Ankylosing Spondylitis, adverse effect, biological agents

Ankylosing spondylitis (AS), a spondyloarthropathy, is a chronic inflammatory arthritis affecting the axial skeleton, sacroiliac joints and nonarticular structures to a different degree. One of the aims of the treatment of AS is to ease the symptoms and nonsteroidal anti-inflammatory drugs (NSAIDs), decreasing the stiffness and pain of inflammation, are the central component of AS treatment, However, many patients with AS have symptoms unresponsive to NSAID treatment and benefit from anti-TNF-α therapy. TNF-α inhibitors etanercept, adalimumab, golimumab, certolizumab and infliximab have proved to be efficient treatment options for patients with AS [1], but might have cause some adverse events including local injection reactions, demyelinating disease, heart failure, hepatotoxicity, malignancy and cytopenias.[2, 3] Although TNF-alpha inhibitors can lead to pancytopenia and occasionally leukopenia as reported in clinical trials, etanercept-induced thrombocytopenia is rarely seen.[4] TNFα regulates some pro-inflammatory cytokines such as interleukin (IL)-1, IL6, IL8 and granulocyte-macrophage-colony-stimulating factor, therefore, in theory, have the potential to block stem-cell differentiation with resultant bone marrow failure. Herein we report a patient who experienced thrombocytopenia induced by etanercept used for treatment of AS.

CASE

Fourty-years-old male patient diagnosed as Axial Spondyloarthritis in 2001, was started on etanercept (25 mg S.C. two times in a week) in April 2017 after failing several DMARDs including methotrexate and sulfasalazine. His pre-treatment blood counts were normal with a platelet count of 155x10^9/l) and he was not using any other drug that could cause thrombocytopenia. After two doses of etanercept his platelet count fell to 79x10^9/l and thrombocytopenia confirmed by examination of peripheral blood smear. His vitamin

Received: *December 30, 2021****; Accepted:*** *January 20, 2022****; Published Online:*** *January 29, 2022*
How to cite this article: *Önmez A, Altun G, Akbaş T, Öneç B. Etanercept-induced thrombocytopenia in a patient with ankylosing spondylitis. DAHUDER M J 2022, 1(1):31-32.*
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B 12 and folate levels were normal, anti-nuclear antibody (ANA) and antibodies to double-stranded DNA (anti-dsDNA) as well as anti-platelet antibodies were negative. Etanercept was discontinued due to the possibility of etanercept induced thrombocytopenia. His platelet count improved 12 days after stopping the etanercept (platelet count 162x10^9/l). There was no finding in the peripheral blood smear to explain other causes of thrombocytopenia. He started on adalimumab, after this treatment he has been no recurrence of the thrombocytopenia or any other side effects.

DISCUSSION

We present a case of patient who experienced pure thrombocytopenia during his treatment with etanercept. Cytopenia, which is also not common, is one of the well-known adverse effects of anti-TNF-α treatment. Hematologic side effects due to etanercept are generally seen as bicytopenia as leukopenia and thrombocytopenia in the literature.[5, 6] Our case is reported as the second isolated thrombocytopenia and the first patient who has AS while under treatment with anti-TNF-α drugs in the literature. The mechanism of anti-TNF-α therapy induced isolated thrombocytopenia is unclear. Several mechanisms have been proposed to explain this. According to a theory, TNF-α regulates some pro-inflammatory cytokines and granulocyte-macrophage colony- stimulating factor (GM-CSF), for this reason this blockage causes block stem-cell differentiation.[7] Another hypothesis is anti-TNF-α treatments contribute to formation of immune complexes, which in turn bind to the surface of platelet cells, so activating the complement cascade and subsequent platelet destruction.8 Another probable mechanisms include a lupus-like syndrome, associated with the production of ANA and anti-dsDNA.[9] The serum lupus antibodies were negative in our case. The temporal connection between the drug administration and the following development of trombocytopenia and between stopping of the drug and analytical recovery was clear. Pathare et al. described a case of isolated thrombocytopenia.[9] Etanercept was discontinued, and the platelet count recovered like other cases. Anti-TNF-α drugs have an important role in the treatment of rheumatic diseases in spite of their hematological side effects. We recommend that routine blood cell count must be performed for detect hematological changes before and shortly after etanercept or other anti-TNF treatment have started.

Authors' Contribution

Study Conception: AÖ,; Study Design: AÖ,; Supervision: GA,; Materials GA,; Literature Review: GA,; Manuscript Preparation: AÖ and Critical Review: BÖ, TA.

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Case Report

Internal Medicine

DAHUDER Medical Journal
e-ISSN: 2791-9250

Lactic asidosis after metformin use in chronic hemodialysis patient

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ABSTRACT

Objectives: Metformin is a biguanide and is used especially in metabolic syndrome where insulin resistance is at the forefront and in Type 2 diabetes mellitus, both by suppressing the endogenous glucose production in the liver and increasing the sensitivity of insulin in peripheral tissues such as fat and muscle tissue.[1] The most rare but life-threatening side effect of metformin is the development of lactic acidosis. Therefore, the glomerular filtration rate is 30 ml/min. its use is contraindicated in patients with chronic kidney disease.[2] Lactic acidosis is the cause of metabolic acidosis with increased anion gap; occurs when the plasma lactate concentration exceeds 4-5 millimol /Liter (mmol /L) (Normal range: 0.5-1.5 mmol /L).[3] Here, we present the development of lactic acidosis due to metformin use in an 84-year-old female patient who has been on chronic hemodialysis treatment for 4 months. The patient applied to the emergency department twice because of confusion. The patient, who was found to have acidosis in the blood gas, regained consciousness after he was taken to hemodialysis and was referred to the nephrology outpatient clinic, considering that she might have dialysis insufficiency. The patient, who learned that she used metformin in his anamnesis, did not recur after the drug was stopped. The use of metformin in advanced age and renal failure may cause fatal complications. Glomerular filtration rate 45 ml/min. metformin should be used with caution in patients with should not be given to those below.

Keywords: metformin, lactic acidosis, type-2 diabetes mellitus, hemodialysis

Metformin is a biguanide and is used especially in metabolic syndrome where insulin resistance is at the forefront and type 2 diabetes mellitus (DM) by suppressing endogenous glucose production in the liver and increasing insulin sensitivity in peripheral tissues such as fat and muscle tissue.[4] Metformin has some advantages over sulfonylureas. For example; It does not cause hypoglycemia, does not increase weight gain and hyperinsulinemia, and contributes positively to blood lipid levels. Because of these advantages, metformin is widely used in the treatment of type 2 diabetics alone or in combination therapy. The most important side effect of metformin is the development of lactic acidosis. Although it is expected that there is a predisposing factor, especially abnormal renal function, lactic acidosis may develop in individuals with normal renal function.[5] Although lactic acidosis due to metformin is a very rare clinical condition, it can be fatal at a rate of approximately 50%.

CASE REPORT

In this case, an 84-year-old female patient was admitted to the emergency department with complaints

Received: *October 30, 2021;* ***Accepted:*** *December 6, 2021;* ***Published Online:*** *January 29, 2022*

How to cite this article: *Biricik M, Bostan F,. Lactic asidosis after metformin use in chronic hemodialysis patient. DAHUDER M J 2022, 2(1):30-32*

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of nausea, dizziness and vomiting for a week. The patient, who was followed up with type-2 diabetes mellitus for 10 years, was using metformin 1000 mg 1*1 and vildagliptin tablet 1*1 in her treatment. In the vital signs checked in the emergency room, TA: 160/80 mmHg, pulse: 90 beats/minute, SpO2; 68 %, respiratory rate 25/minute. Laboratory parameters were as follows: PH: 7.12 mmHg, HCO3: 10.50 mmol/L, PCO2: 33.0 mmHg, SO2: 53.60 %, BE: -17.4 mmol/L, and c-lac: 13.0 mmol/L. The patient, whose general condition was moderate, conscious and oriented-cooperative, was admitted to the ward. In other tests, wbc: 22,4 10*3/uL, CRP: 9 mg/L, BUN: 94 mg/dL, creatinine: 5.7 mg/dL and blood glucose: 147 mg/dL (table 1). The patient is on hemodialysis 3 days a week. The patient's acidosis and clinic did not improve despite hemodialysis. According to the information received from the relatives of the patient, the patient was using 1000 mg of metformin. Metformin was stopped and crystallized insulin was administered to the patient according to her blood glucose. In the follow-ups, the patient whose acidosis and clinical condition improved in arterial blood gas, and whose lactate level returned to the normal range, was prescribed insulin and the patient was discharged with full recovery.

CONCLUSION

Metformin-induced lactic acidosis is a rare, preventable, but life-threatening side effect when it develops. Its total incidence has been reported as 2-9 cases per 100,000 patients per year.[6, 7] Especially in the presence of renal dysfunction, lactic acidosis may develop due to metformin use. However, the fact that there are very few cases reported to date, leads to the fact that lactic acidosis developing due to metformin is easily missed, especially in individuals without renal dysfunction. We think that this oral antidiabetic drug, which is widely used today, should be used by evaluating the complication risks for selected patients. In our case, metformin-induced lactic acidosis developed in the presence of renal failure. In the presence of renal insufficiency, the clearance of both lactate and metformin decreases and the risk of lactic acidosis increases.[8] Therefore, metformin should not be started in patients with creatinine levels higher than 1.4 mg/dL in women and 1.5 mg/dL in men. The development of severe metabolic acidosis without ketosis in patients treated with biguanides was first reported by Walker and Linton in 1959, and the precursor of metformin, phenformin, was withdrawn from the market in 1982 due to its high lactic acidosis-inducing effect. Lactic acidosis is a clinical emergency that requires prompt diagnosis and prompt treatment. A 42.5% mortality rate was reported in the series of Misbin *et al*.[9] Recovery is possible even in very serious cases, thanks to early diagnosis and prompt initiation of treatment. It has been reported that especially patients with chronic renal failure benefit from dialysis.[10] As a result, metformin, which can be used alone or in combination in the treatment of type 2 DM, has the potential for side effects such as lactic acidosis, especially due to its positive effects on insulin resistance. We believe that in the absence of absolute contraindications, there is no obvious reason to deny patients clinical benefits

Table 1. Laboratory parameters of the patient while using metformin and after discontinuation

Parameter	When using	After stopping
WBC (10*3/uL)	22.4	18.3
BUN (mg/dL)	94	41
Creatinine (mg/dL)	5.7	2.3
Glucose (mg/dL)	147	118
CRP (mg/L)	9	9
PH (mmHg)	7.12	7.29
PCO2 (mmHg)	33	36
HCO3 (mmol/L)	10.5	18.1
Lactate (mmol/L)	13.0	2.7
SPO2 (%)	68	92

of metformin therapy. Clinicians who start metformin treatment should assess renal function and instruct patients to discontinue the medication and consult their doctor in case of severe vomiting and/or diarrhea, or other hypovolemic conditions. Although it is a very rare and preventable side effect, it can be a mortal side effect when patient selection is not done well. For this reason, we recommend that it should not be preferred in patients with type 2 diabetes who are at an advanced age and have serious diabetic complications.[11]

Authors' Contribution

Study Conception: MB,; Study Design: MB,; Supervision: MB,; Materials: FB,; Data Collection and/or Processing: MB,; Funding: FB,; Statistical Analysis and/or Data Interpretation: FB,; Literature Review: MB,; Manuscript Preparation: FB and Critical Review: FB.

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