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Drug reactions in children with rheumatic diseases receiving parenteral therapies: 9 years' experience of a tertiary pediatric rheumatology center

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Abstract

Parenteral treatments (either subcutaneous or intravenous) are frequently used in rheumatology practice. In this study, drug side effects in patients who were followed up with a rheumatic disease and treated with parenteral administration methods were evaluated. The drug side effects in children who were followed up with a rheumatic disease and treated with parenteral treatments between 2010 and 2019 were recorded, retrospectively. All parenteral treatments are applied by a clinical nurse specialist (CNS) who is experienced in pediatric rheumatology for 10 years. Four hundred and thirteen patients were evaluated in this study. The mean age was 12.09 ± 5.05 years. Most of them were diagnosed with juvenile idiopathic arthritis ($n = 317$) and colchicine-resistant familial Mediterranean fever ($n = 57$). Among the patients, 287 was treated with methotrexate, 130 with etanercept, 90 with adalimumab, 71 with anakinra, 64 with canakinumab, 55 with tocilizumab, seven with rituximab, six with infliximab, and four with abatacept. Two of the patients had a history of drug allergy (ceftriaxone = 1, ranitidine = 1). The most common adverse reactions were as follows: nausea–vomiting in 52, rash in 11, itching in three, chest tightening in two, bruising in two, headache in two, and abdominal pain in one of the patients. Drug side effects were observed after an average of three (1–4) administrations. Antihistaminic and steroids (tocilizumab = 3, infliximab = 1, methotrexate = 1) were administered to five patients due to hypersensitivity reactions. Considering the possible side effects and preparation protocols of parenteral treatments, experienced physicians and nurses are required in the field.

Keywords Pediatric rheumatology · Parenteral therapy · Adverse reactions · Clinical nurse specialist

Introduction

Pediatric rheumatology is a subspecialty of pediatrics providing comprehensive care to children (as well as their families) with various kinds of autoimmune and autoinflammatory diseases. With the advantages in the pharmaceutical industry, many drugs for rheumatologic diseases have been developed in recent years. However, many of these drugs [(disease-modifying drugs (DMARDs) and biologic drugs (BDs)] require parenteral administration and

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require special preparation and administration techniques. Therefore, experienced healthcare professionals are required for the application of these medications. The most frequently used parenteral DMARD in children is methotrexate, while almost all biologic drugs, including anakinra, canakinumab, etanercept, adalimumab, infliximab, abatacept, tocilizumab, and rituximab, are administered parenterally. Among them, anakinra is an anti-interleukin 1 receptor antagonist [1], canakinumab is a monoclonal anti-interleukin 1 antibody [1], etanercept (a fusion protein), adalimumab (monoclonal antibody) and infliximab (monoclonal antibody) are all antitumor necrosis factor alpha (TNFα) drugs [2], abatacept is an anti-CTLA4 fusion protein [3], tocilizumab is a monoclonal anti-interleukin 6 antibody [4], and rituximab is an anti-CD20 antibody [5].

Clinical nurse specialists (CNSs) provide care to patients in a number of specialties. They are involved in the management of diseases by participating in both medical therapy and psychosocial issues of patients. They support other health professionals to improve patient care. The fundamental goal of CNS is to provide safe, qualified, and cost-effective specialty care. In the last 50 years, pediatric rheumatology had been recognized as a separate discipline all over the world. The emergence of rheumatology as a discipline in pediatrics has initiated the training of specialists in this field. CNSs in the field of pediatric rheumatology may facilitate the management of children by contributing to the treatment strategies of the physicians. This participation seems to lessen the inaccuracies of storage, preparation, and administration of medications.

In this study performed at a tertiary pediatric rheumatology unit, we aimed to put forth and share 9 years' experience of drug reactions occurring after the application of parenteral medications to children with rheumatic diseases by a CNS.

Materials and methods

Children (aged 0–18 years) who were diagnosed with a rheumatic disease and received a parenteral treatment during their disease course were included to the study. Demographic data and treatments were documented from the patients' files. The study consists of patients who were followed between May 2010 and January 2019. All parenteral treatments were first applied by a specialist nurse (RK) in the pediatric rheumatology infusion unit where services between Monday and Thursday from 8:00 am to 4:00 pm. The parenteral treatments were administered either subcutaneously (methotrexate, anakinra, canakinumab, etanercept, and adalimumab) or as an infusion (abatacept, infliximab, methylprednisolone, rituximab, and tocilizumab) by following the manufacturer's instructions. To diminish the injection-site reactions, patients who were treated with a subcutaneous treatment were educated by a specialist nurse (RK). Warming the syringe before the injection, applying a cold pack to injection site 2–3 min before and immediately after the injection, and alternating the injection sites were recommended to all patients and their parents who were treated with subcutaneously administered drugs. The nurse evaluated the patients' vital signs every 15 min during the first hour of the infusion, every 30 min during the second hour of the infusion, and every 60 min thereafter. All suspicious complaints and findings were recorded by a specialist nurse (RK) who has been working in a pediatric rheumatology infusion unit for 10 years. All suspicious reactions due to a parenteral treatment were reported immediately to the pediatric rheumatologists (NAA, MÇ, HES). All patients were questioned about the presence of all the signs and symptoms regarding systemic evaluation. Furthermore, drug reactions rising after the introduction of subcutaneous drugs were recorded by face-to-face interviews in every control and by phone calls.

Folic acid supplementation (1 mg/2 days of the week) was recommended at least 24 h after the weekly dose of MTX. All patients were screened for existing latent and active tuberculosis at the initiation of the therapy and every 6 months. Tuberculin skin test (TST) and chest X-rays were performed. A positive TST result was accepted as a reaction of ≥ 5 mm. Furthermore, infections requiring hospitalization were recorded.

The study was reviewed and approved by the ethical review committee of Kanuni Sultan Süleyman Research and Training Hospital. Patients' files were evaluated retrospectively and all patients were anonymous. When the patients were admitted to the hospital, the parents gave general consent approving anonymous data use for academic purposes.

Statistical analyses

Statistical analyses were performed using the SPSS software version 21. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using proportions, mean, standard deviation (SD), medians, minimum (min), and maximum (max) values as appropriate.

Results

A total of 413 patients receiving parenteral therapy were included into the study group. Among them, 205 (49.6%) were female and 208 (50.4) were male. The mean ± SD age was 12.09 ± 5.05 years. Among them, 317 (76.7%) patients

were diagnosed with juvenile idiopathic arthritis (JIA), 57 (13.8%) patients with colchicine-resistant familial Mediterranean fever (FMF), ten (2.4%) patients with mevalonate kinase deficiency (MKD), seven (1.6%) patients with systemic lupus erythematosus (SLE), six (1.4%) patients with cryopyrin-associated periodic fever syndrome (CAPS), three (0.7%) patients with systemic sclerosis (SS), three (0.7%) patients with juvenile dermatomyositis (JDM), three (0.7%) patients with chronic recurrent multifocal osteomyelitis (CRMO), three (0.7%) patients with adenosine deaminase 2 deficiency (DADA2), two (0.4%) patients with Takayasu arteritis (TA), one (0.2%) with Behçet's disease (BD), and one (0.2%) with Sjogren's syndrome. Furthermore, 31 (7.5%) JIA patients had also FMF.

Among these patients, 287 (69.4%) received methotrexate, 130 (31.4%) received etanercept, 90 (21.7%) received adalimumab, 71 (17.1%) received anakinra, 64 (15.4%) received canakinumab, 55 (13.3%) received tocilizumab, seven (1.6%) received rituximab, six (1.4%) received infliximab and four (0.9%) received abatacept. Eighty-five (20.5%) patients used more than one biological treatment during their disease course. One hundred and eighteen patients were using methotrexate concomitant to biological treatment. From 2010 through 2019, a total of 1722 infusion treatments were applied in our pediatric rheumatology infusion unit (Fig. 1). Furthermore, a total of 41,113 subcutaneous treatments were applied (Fig. 2).

Only two of the patients had a history of previous drug allergy (ceftriaxone = 1, ranitidine = 1). Drug reactions were observed in 66 (15.9%) patients as follows: nausea and vomiting in 52 (78.8%), rash in 11 (16.6%), itching in three (4.5%), chest pain in two (3%), bruising in two (3%), headache in two (2.5%), abdominal pain in one (1.5%), tingling in the throat in one (1.5%), and paradoxical psoriasis in one (1.5%) (Table 1). Drug side effects were observed after a median (min–max) of 3 (1–4) administrations. Five (7.5%) patients (tocilizumab = 3, infliximab = 1, methotrexate = 1) were treated with antihistaminic drugs and steroids due to the hypersensitivity reaction. Additionally, one (1.5%) patient receiving tocilizumab required adrenalin. The drug reactions of the patients were summarized in Table 1.

Methotrexate was ceased due to gastrointestinal intolerance in 36 patients and due to allergic skin reactions in one patient then switched to leflunomide. Tocilizumab treatment was stopped in three patients due to allergic reactions. Infliximab was discontinued in one patient due to allergic reactions. Anakinra was switched to canakinumab in eight patients due to local injection-site reactions. For one patient with paradoxical psoriasis application for obtaining secukinumab was made to the ministry of health.

Two patients receiving anti-TNF drugs had reactivation of tuberculosis. A 14-year-old girl with polyarticular JIA and receiving adalimumab was diagnosed with tuberculosis at the 18th month of adalimumab initiation. At the time of adalimumab initiation, the tuberculin skin test was 0 mm and chest radiography was normal. Subsequently, she was admitted to the outpatient clinic with a cough lasting for one month. Tuberculin skin test was 9 mm and thorax tomography was revealing paratracheal, subcarinal, and hilar lymphadenopathies, infiltration areas in the right lung, ground glass density nodules and centrilobular opacities. Acid-fast stain was positive in the sputum of the patient. A 17-year-old boy with polyarticular JIA receiving adalimumab was diagnosed with tuberculosis at the 16th month of adalimumab

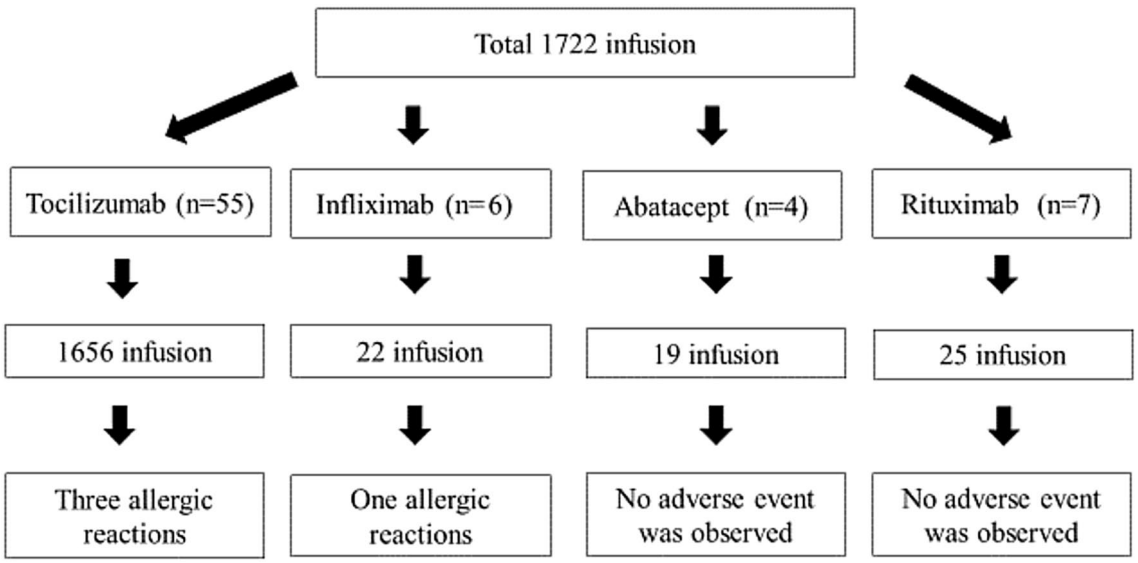

Fig. 1 Distribution of patients with rheumatic diseases receiving infusion treatments

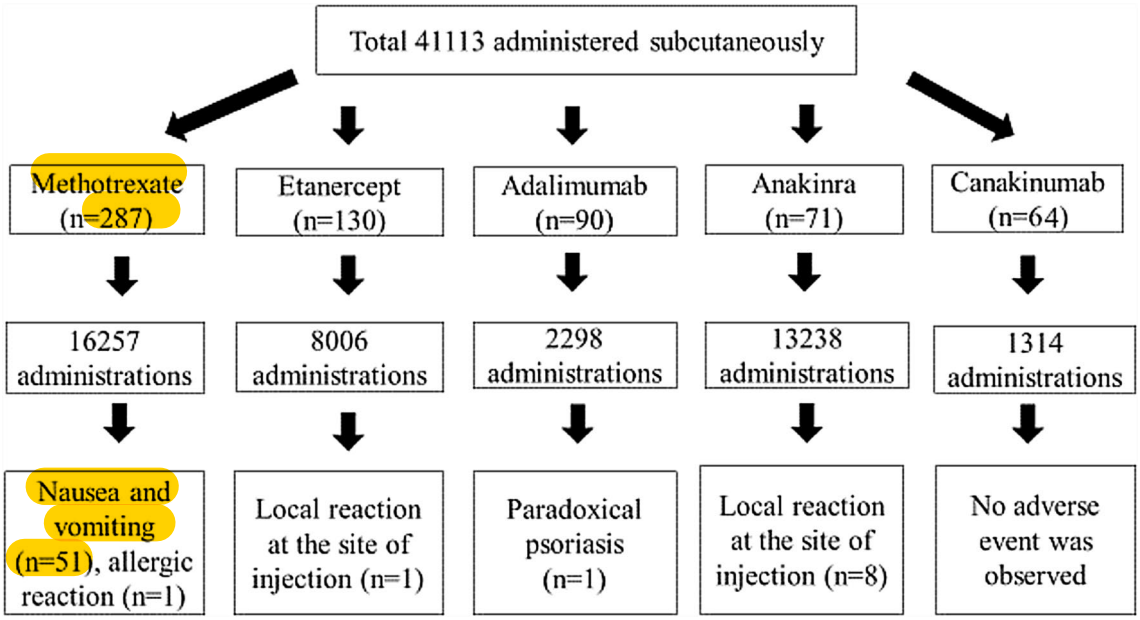

Fig. 2 Distribution of patients with rheumatic diseases receiving subcutaneous treatments

Table 1 The drug reactions of the patients with rheumatic diseases receiving parenteral treatments

Drug reactions	Drugs
Nausea and vomiting ($n=52$)	Methotrexate ($n=51$), tocilizumab ($n=1$)
Rash ($n=11$)	Adalimumab ($n=1$), anakinra ($n=8$), etanercept ($n=1$), tocilizumab ($n=2$)
Chest pain ($n=2$)	Methotrexate ($n=1$), tocilizumab ($n=1$)
Bruising ($n=3$)	Infliximab ($n=1$), tocilizumab ($n=2$)
Headache ($n=2$)	Methotrexate ($n=2$)
Itching ($n=3$)	Adalimumab ($n=1$), anakinra ($n=1$), methotrexate ($n=1$)
Tingling in the throat ($n=2$)	Infliximab ($n=1$), tocilizumab ($n=1$)
Abdominal pain ($n=1$)	Methotrexate ($n=1$)

initiation. Tuberculin skin test was 15 mm at the time of adalimumab initiation. However, chest radiography was normal. He was given isoniazid prophylaxis for nine months and adalimumab was started at the first month of isoniazid prophylaxis. He was admitted to the outpatient clinic with cough and fever at the 16 months after the first dose of adalimumab injection. His sputum was positive for acid-fast stain, as well. Both of them started with anti-tuberculosis therapy and adalimumab was ceased.

Discussion

A total of 1722 infusions and 41,113 subcutaneous treatments were applied for 9 years and drug reactions were observed in 66 (15.9%) patients. Among them, 52 patients suffered from nausea and vomiting, nine patients had a local reaction at the injection site, five had severe hypersensitivity reactions requiring medications and one had paradoxical psoriasis.

Modern therapeutics have dramatically changed the management of children with rheumatic diseases. Although we are now more successful in controlling rheumatic diseases, new problems have emerged along with new treatment approaches. For instance, all the parenteral medications for rheumatic diseases require special application and preparation protocols [6]. Subcutaneously administered medications may be administered daily, weekly, or biweekly. Most families want to apply these drugs themselves, as it will be difficult to come to the hospital for all applications. In such cases, travel burden, inaccuracies of storage and preparation, and incompliance may reduce the response of the prescribed medication. Therefore, all parents/patients need education for careful application and regular monitoring of drug administration. A total of 41,113 subcutaneous treatments were applied for 9 years. Among them, 62 drug reactions

were documented. MTX-related nausea and vomiting were the most common drug reaction. Previous studies demonstrated that 11–43% of patients receiving MTX suffered from vomiting [7, 8]. Subcutaneous administration with folate supplementation may reduce the side effects [9]. All the patients treated with MTX were educated for side effects. A total of 16,257 MTX injections were applied to 287 patients during 9 years' period and nausea–vomiting was observed in 51 patients (17.7%) despite subcutaneous administration with folate supplementation. The injection-site reaction is another common drug reaction in patients receiving subcutaneously administered medications. The rate of injection-site reactions was reported as 15–20% for adalimumab, 29–37% for etanercept and 50–80% for anakinra [10] previously. However, we observed only eight local reactions due to anakinra and one due to etanercept. Warming the syringe before the injection, applying a cold pack to injection site 2–3 min before and immediately after the injection and alternating the injection sites may be the reason of low frequency of local reactions. Singh et al. [11] conducted a meta-analysis about potential adverse effects of biologic drugs. They demonstrated that infliximab was associated with a statistically significant higher rate of total adverse events and withdrawals due to adverse events compared with the other biologic drugs. Certolizumab pegol and anakinra were associated with a statistically significantly higher risk of serious infections compared with the other biologic drugs [11]. Only two of our patients receiving adalimumab had reactivation of tuberculosis. None of our patients had infections that required hospitalization. de Camargo et al. [12] reported that the most frequent drug reactions were injection-site reactions (27.2%) followed by infections (11.2%) in psoriatic arthritis and rheumatoid arthritis patients receiving BA. However, they could not demonstrate a predisposing factor associated with drug reactions [12].

Furthermore, hypersensitivity reactions may occur during the infusion applications. Previously, hypersensitivity infusion reactions have been reported in 5–10% of patients treated with rituximab [13] in 6.9% of patients receiving tocilizumab [14] and 2–3% of patients treated with infliximab [15]. Recently, Weiner et al. evaluated the knowledge of rheumatology fellows about acute infusion reaction management and unfortunately, they found that training programs and applications about infusion reactions were insufficient during rheumatology education [10]. Most recently, Vinod et al. [16] reported 3 years of experiences of a pediatric rheumatology infusion center, 7585 intravenous infusions were applied to 398 patients, and 41 infusion reactions in 34 patients were documented. In our center, pediatric rheumatology infusion unit serves a qualified approach by a CNS nearly 10 years. A total of 1722 infusions were applied and four allergic reactions were documented requiring antihistaminic drugs and steroids. Furthermore, one patient receiving MTX had a hypersensitivity reaction and was treated with antihistaminic drugs and steroids.

Our study was limited by single-center and retrospective design. However, the same experienced CNS was dealing with all the patients for an extended period of time and the data were collected homogeneously by the same person according to a standard protocol. As far as we know, there is only one study reporting intravenous infusion reactions of a single pediatric rheumatology center [16], but our study involves drug reactions after both intravenous infusions and subcutaneous injections for a longer period of time.

In conclusion, an experienced CNS may improve the adherence of the patients to the treatment protocol, provide education about safe injection techniques, and warn them of the potential drug reactions of parenteral injections. Using standardized infusion protocols and combining experiences of physicians and nurses may provide an effective management and satisfying outcome in chronic rheumatic diseases.

Author contributions RK conceptualized and designed the study, drafted the initial manuscript, and had full access to all the data in the study; HES designed the study, conducted the data analyses, drafted the initial manuscript, and had full access to all the data in the study; AT, FÇ, and MÇ drafted the initial manuscript; NAA conceptualized and designed the study, drafted the final manuscript, and had full access to all the data in the study and all authors reviewed and revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest None.

Ethical approval The study was reviewed and approved by local ethical committee (Ethics approval number: KAEK/2019.01.06).

Informed consent All these patient files were evaluated retrospectively and all patients were anonymous. When the patients admitted to the hospital, the parents/patients gave a general consent approving anonymous data use for academic purpose.

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