Journal of Pre-Clinical and Clinical Research 2024, Vol 18, No 1, 16-20
www.jpccr.eu

CASE REPORT

A case of concomitant juvenile idiopathic arthritis (JIA) and paediatric-onset multiple sclerosis (POMS) – treatment with secukinumab and dimethyl fumarate followed by ofatumumab

Aleksandra Jartych[1,A-D]✉, Anna Jamróz-Wiśniewska[1,A,E-F], Konrad Rejdak[1,E-F], Weronika Kleszczyńska[1,C-D], Michał Kaczor[1,B-D]

[1] *Department of Neurology Medical University, Lublin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Jartych A, Jamróz-Wiśniewska A, Rejdak K, Kleszczyńska W, Kaczor M. A case of concomitant juvenile idiopathic arthritis (JIA) and paediatric-onset multiple sclerosis (POMS) – treatment with secukinumab and dimethyl fumarate followed by ofatumumab. J Pre-Clin Clin Res. 2024; 18(1): 16–20. doi: 10.26444/jpccr/185685

Abstract

The aim of this case report is to highlight new possible treatment methods for concomitant juvenile idiopathic arthritis and multiple sclerosis in young patients. Promising results of using ofatumumab, secukinumab and dimethyl fumarate, both in the clinical case of a 22-year-old patient and mentioned literature, allows the belief that there is a chance for improving the quality of life of those who suffer from coexisting autoimmune diseases. However, it is crucial to perform further research in terms of the necessity and safety of the mentioned therapies, especially in the paediatric population, among whom there often exists difficulty in using treatment not registered for under-aged patients. Furthermore, the higher risk of side-effects caused by combined treatment of two autoimmune diseases should also be taken into consideration.

Key words

juvenile idiopathic arthritis, autoimmune diseases, ofatumumab, dimethyl fumarate, multiple sclerosis, secucinumab

INTRODUCTION

Juvenile idiopathic arthritis (JIA) and paediatric-onset multiple sclerosis (POMS). Juvenile idiopathic arthritis (JIA) is an idiopathic and heterogeneous disease manifesting in adolescents up to the age of 16, with sSymptoms of joint inflammation lasting for more than six weeks. The causes of the disease's manifestation are still unexplored. Infection with Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), Varicella zoster virus (VZV), Chlamydia pneumoniae and Helicobacter pylori bacteria are believed to be potential risks for the condition [1]. Breastfeeding, however, has been shown to be potentially protective, reducing the incidence of autoimmune diseases, including JIA. Breastfeeding increases the number of commensal intestinal bacteria as well as being rich in IgA, reducing the chance of intestinal infections, which has beneficial effects on the development of the intestinal microflora [2]. Genetic factors also play a role in the development of both JIA and multiple sclerosis (MS). The specific HLA antigens HLA-DRB1*15 and HLA-DQB1*06:02 are associated with an increased risk of MS, in contrast to HLA-DRB1*01, HLA-DRB1*09, HLA-DRB1*11 or HLA-DRB1*12, among which protective marks are seen [3].

JIA is the most common rheumatologic condition among minors, with the incidence estimated at about 1.6–23/100,000 children, depending on the country. The most common subtype is sclerosing JIA (50%-60%), followed by polyarthritis (30%-35%) and systemic (10%-20%) [4]. In diagnostic imaging, MR imaging (MRI) and ultrasound are routinely used to assess damage to the patient's joint. Rheumatoid factor and HLA-B27 are also determined to assign symptoms to the correct subtype.

The main symptom of JIA is inflammation of the joints, manifested by swelling, soreness, and restriction of mobility. Initially, the inflammatory process involves the synovial membrane, and with the progresses of the disease, spreads to the muscles, tendon attachments and bone epiphyses. The therapeutic goals in the treatment of JIA are to return the patient to the activities of daily living to prevent low-growth, as well as the patient's disability. In addition, prevention of complications of the eye and other internal organs is important [4].

Multiple sclerosis (MS) is a progressive neurodegenerative disease of the central nervous system which most often affects people between ages of 20 – 40. Children suffer from it relatively rarely with 3 – 10% of the MS population experiencing the first symptoms before the age of 18. Risk factors for the development of Paediatric-Onset Multiple Sclerosis (POMS) include, as in JIA, viral infections (most often the EBV virus), vitamin D3 deficiency, and passive smoking. The hormonal system also plays a role in the pathogenesis of the disease, which probably contributes to the more frequent occurrence of POMS in girls. The most common type of MS in the paediatric population is the

✉ Address for correspondence: Aleksandra Jartych, Department of Neurology, Medical University, Jaczewskiego 8, 20-954 Lublin, Poland
E-mail: aleksandrajartych@gmail.com

Received: 13.02.2024; accepted: 05.03.2024; first published: 18.03.2024

relapsing-remitting type (RRMS) which usually manifests itself with motor and/or sensory dysfunctions and cerebellar syndrome. Compared to adults, children experience more frequent relapses of the disease, which in turn increases the risk of physical disability later in life. Diagnostics consists primarily of a thorough interview, neurological examination and imaging of demyelinating brain lesions using MRI. The diagnosis, similarly to MS, is based on the McDonald criteria which demonstrate dissemination in time and space. In the treatment of POMS, methylprednisolone for relapses and interferon beta, dimethyl fumarate (DMF) and fingolimod are used as immunomodulating therapy [5–7].

CASE REPORT

The case is presented of a 22-year-old patient diagnosed with JIA in 2015 and with MS in 2018. The first symptoms of the musculoskeletal system appeared at the turn of 2015 and 2016. The 15-year-old boy complained then of pain in the right ankle, right knee, left wrist and right sacroiliac joint. Additionally, he reported morning stiffness of the above-mentioned joints with improvement after movement, and increased pain at night. A few months earlier, he had suffered from parotitis and a gastrointestinal infection with diarrhoea and severe abdominal pain. In the family history, his grandmother suffered from psoriasis.

An MRI of the spine performed in 2016 revealed a small bulge of the dural sac at the levels L2/3, L3-L4, L4-L5, L5-S1 and inflammatory changes in the intervertebral joints of the lumbar section. During this time, joint pain symptoms were accompanied by positive radicular symptoms and a disturbance of superficial sensation (hyperesthesia) on the right side on the outer surface of the thigh. A diagnosis of sciatica was made and treatment with diclofenac and tolperisone was initiated. Unfortunately, the symptoms did not subside.

In March 2016, the patient was admitted to the Paediatric Rheumatology Department due to persistent pain in the joints and lumbosacral area. The laboratory tests performed revealed the presence of the HLA-B27 antigen, increased inflammatory parameters and the presence of IgM and IgG antibodies towards Yersinia enterocolitica. A diagnosis of reactive arthritis was made. The treatment included ciprofloxacin, sulfasalazine, non-steroidal anti-inflammatory drugs, and small doses of steroids with gradual improvement.

At the end of 2016, the pain returned, and in March 2017, it was planned that the patient would be treated with methotrexate. The tests performed at that time showed a positive Quantiferon TB Gold test twice. In April, isoniazid was added to the treatment. Control MRI of the spine revealed features of wide-base protrusion of the intervertebral discs with moderate pressure on the dural sac and moderate bilateral narrowing of the intervertebral foramina at the levels L3/L4, L4/L5, L5/S1. MRI of the sacroiliac joints performed a month later showed signs of inflammation of both sacroiliac joints and moderate oedema changes in the subchondral layer of the hip bone on the right side. Due to persistent inflammation, methotrexate was started in June 2017 and remission achieved.

In March 2018, the patient developed new symptoms. Neurological examination revealed decreased muscle strength and temperature sensation in the right upper limb and right lower limb, asymmetric gait with right foot drop, and excessive tendon reflexes on the right side. There was deterioration of the motor function of the right hand and cooling of the skin of the right forearm. The boy did not report any joint pain. Anti-inflammatory treatment was discontinued during the tests carried out in the paediatric neurology department.

In the meantime, the sensory disturbances moved from the right to the left side of the body, and a positive Babinski sign appeared on the right side. In the Expanded Disability Status Scale (EDSS) he received 4 points.

MRI of the brain and spine revealed numerous demyelinating lesions (10 paraventricular and periventricular demyelinating lesions, a few subcortical lesions, and two lesions within the corpus callosum) [Figure 1]. Based on the clinical picture and MRI, MS was diagnosed and steroid pulses were administered; interferon beta-1b therapy was then introduced. Due to the increase in liver enzyme levels, methotrexate was discontinued. In July 2018, the joint symptoms recurred and methotrexate was reintroduced. In January 2019, the dose was increased to 17.5 mg/week. When the patient turned 18, he was referred to the Rheumatology Clinic for Adults, where he continued treatment and rehabilitation. Due to the lack of sufficient response to the rheumatological treatment (oral steroids, methotrexate, celecoxib), swelling and pain in the joints of the lower limbs and limited mobility, steroids were excluded from the treatment, and secukinumab was added.

The patient was also referred to the Neurology Clinic for Adults. Since the original diagnosis of MS in 2018, no relapses of the disease have occurred. In 2019, because of poor tolerance of interferon beta-1b injections, the treatment of MS was switched to dimethyl fumarate (DMF). During the next three years the patient was neurologically stable, and on MRI of the brain no new demyelinating lesions were observed.

In 2023, however, due to persistent side-effects associated with DMFuse – abdominal pain, diarrhoea, burning and redness of the skin of the face and hands – it was decided to discontinue administration of the drug. The treatment was switched to ofatumumab – a human monoclonal antibody against CD20 antigen. After several months of ofatumumab use, the patient noticed relief from the side-effects of his previous treatment. Nevertheless, he also reported decreased sensation and muscle strength on the right side of his body and paroxysmal tingling, especially in the right lower limb, and frequent fatigue.

MRI of the brain performed in March 2023 revealed no new demyelinating lesions. In 2024, the patient's neurological condition remains stable. In the EDSS scale, the patient's neurological condition is assessed at 1.5 points.

DISCUSSION

Treatment of JIA with concurrent MS in young patients. Although many cases of the coexistence of rheumatoid arthritis (RA) and MS have been described, only a few cases have been reported of the coexistence of JIA and MS. Chighizola et al. presented two clinical cases of young female patients with the oligoarticular form of JIA, who were also diagnosed with MS. Both patients were treated with methotrexate and biological drugs (anti-TNF) before the diagnosis of MS, after which neurological symptoms

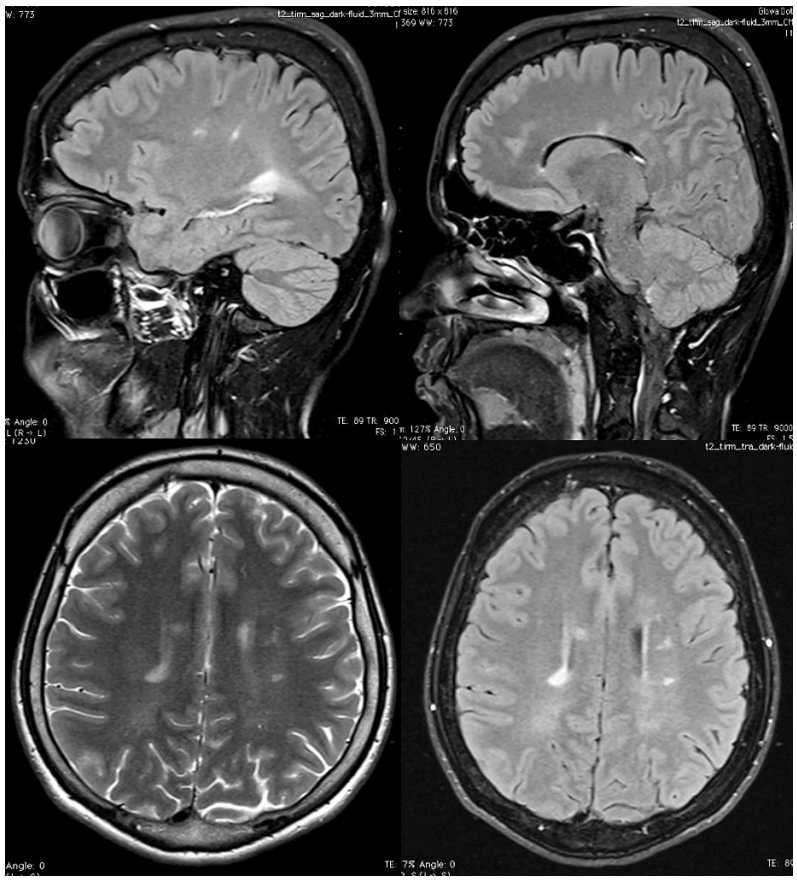

Figure 1. MRI of the patient's brain showing demyelinating lesions in the white matter – sagittal view (upper row), transverse view (bottom), T2-weighted images

occurred, including dizziness and paresthesia. Cerebrospinal fluid examination and MRI confirmed MS in both women; steroid pulses were introduced which alleviated the neurological symptoms.

Based on the two cited clinical cases, a cautious conclusion can be drawn that anti-TNF drugs may be associated with the development of MS symptoms in JIA patients which, in turn, would suggest that MS is a complication of rheumatological treatment. However, due to insufficient data, it is extremely difficult to determine what mechanism exists between the common course of JIA and MS. Potential methods of treatment still remain unknown and therefore present a great challenge for clinicians [8].

Single cases of the coexistence of JIA and the demyelinating disease of CNS in paediatric population have also been reported. A young female patient suffering from cerebral palsy and epilepsy, described by Coşkun A.N. et al., was diagnosed with JIA at the age of 9 years. During treatment with methotrexate, the patient presented motor deterioration, dysphasia and loss of vision. Based on the symptoms, the presence of demyelinating lesions on MRI and the presence of oligoclonal bands in the CSF, she was diagnosed with the primary demyelinating disorder. Intravenous treatment followed by oral administration of methylprednisolone produced clinical improvement, MRI regression, and absence of new lesions [9].

In 2006, the Polish authors Pruszkiewicz M. et al. described a 31-year-old female patient with concomitant MS and juvenile arthritis. Effective therapy with interferon-beta and methylprednisolone had no major side-effects [10].

The 22-year-old patient in the presented Case Report was diagnosed with JIA in 2015 and MS in 2018, and treated with secukinumab with dimethyl fumarate, followed by secukinumab with ofatumumab, which resulted in a promising improvement in the patient's clinical condition.

Use of secukinumab. Secukinumab is a recombinant human monoclonal antibody directed against interleukin 17 (Il-17), which is used in the treatment of psoriatic arthritis (PsA). Clinical trials FUTURE 1–5 have shown high effectiveness of this drug in combatting the symptoms of arthritis, as well as extra-articular symptoms (enthesitis, dermatological changes) in people with PsA and other inflammatory spondyloarthropathies [11]. In a 52-weeks long randomised study conducted by Baraliakos X et al. among 498 patients with PsA, 167 patients took 300 mg of secukinumab, 165 patients – 150 mg of secukinumab, while the remaining patients took placebo. Patients taking secukinumab showed significant improvement in symptoms of axial disease (ASAS20 response) compared to patients taking placebo [12]. Secukinumab has also been proven to be a drug that is well tolerated and improves health-related quality of life (HR-QOL) [13]. However, attention should be paid to the side-effects of anti-Il-17 antibodies. Some of the most common are oral candidiasis, respiratory tract infections and inflammatory bowel disease. Additionally, subcutaneous injections of secukinumab increase the risk of local painful skin swelling and allergic reactions [14].

Use of DMF. DMF is an ester of fumaric acid that activates the transcription pathway of the nuclear factor NRF2.

Currently, it is used to treat Relapsing Remitting MS (RRMS) and psoriasis. Vermersch P. et al. conducted research on 150 patients with RRMS under 18 years of age, among whom 78 received DMF and 72 received interferon beta. After week 96 of the study, it was shown that 66.2% of patients taking DMF did not experience a disease relapse, compared to 52.3% of patients taking interferon beta. Moreover, 16% of patients taking DMF did not show T2-weighted hyperintense lesions on imaging, compared with 4.9% of patients taking interferon beta [15]. The anticancer properties of DMF have also been proven – inhibition of the growth of cancer cells in the course, among others, of T-cell lymphoma, lung adenocarcinoma and cervical cancer [16]. Clinically important side-effects of DMF may be lymphopenia and an increased risk of progressive multifocal leukoencephalopathy (PML). Moreover, many patients complain of gastrointestinal discomfort, nausea or flushing [17, 18].

Potential benefits of concomitant use of secukinumab and DMF. In the current literature review, there are few articles on the use of secukinumab in combination with DMF in patients with two different autoimmune diseases. The first study on the combination of these drugs was conducted by Di Tullio et al. in a 44-year-old patient with psoriasis, psoriatic arthritis and RRMS. Satisfactory results were obtained – no neurological symptoms, reversal of joint pain, and complete disappearance of skin symptoms (Psoriasis Area and Severity Index-100) [19]. This allows conclusions to be drawn about the potential advantages of using the above-mentioned drugs in patients with other autoimmune diseases. However, more evidence of the safety of such therapy and a detailed assessment of benefits and deficits are needed.

Use of ofatumumab. Ofatumumab is a human monoclonal antibody against the CD20 antigen, localised on B lymphocytes. This substance is used in the treatment of chronic lymphocytic leukaemia among patients with a poor prognosis [20]. In the two-phase, three-months APLIOS study (NCT03560739) conducted on 284 patients taking ofatumumab, it was shown that in the 12th week of the study, in as many as 98.2% of patients, the concentration of B lymphocytes was <10 cells/microliter [21]. These cells play a key role in the pathophysiology of MS, therefore the use of the product is considered for the treatment of the projective forms of MS, with the active form of the disease being proven by clinical or imaging studies.

As reported by Sauer et al., ofatumumab shows an advantage over teriflunomide as it demonstrates a lower rate of worsening of the disability, from 8.1% – 12.05%. The same study reported that levels of the neurofilament light chain (NfL), which is a biomarker of neurofibrillary damage, decreased significantly [22]. The percentage of patients who had no clinical evidence of disease activity but had MRI changes was 23.5%, respectively, in year one, declining to 14.8% in year seven. Among patients studied by Bar-Or et al. who took ofatumumab, favourable changes in gadolinium MRI scans were shown among 64.2% at baseline and 94.1% at week 12, respectively [21].

The most common non-locally related side-effects of ofatumumab include acute inflammation of the upper respiratory tract, headache and urinary tract infections [23]. Due to the subcutaneous method of drug administration, some patients developed local inflammatory reactions, manifested as itching or swelling. The subcutaneous form of administration of the drug (thigh, abdomen, upper external part of the arm), makes it gain in value, allowing self-administration of the drug at home by the patient,.

Taking into account the effect of the drug – impairing the humoral immune response – it should not be included in the therapy in the case of an acute condition in the patient [24].

Other contraindications to the drug, including acute hepatitis B, studies have reported cases of fulminant hepatitis in cases of ofatumumab treatment, in which in doses higher than those recommended were adsministered. Excessive doses of the product may also result in progressive multifocal leukoencephalopy (PML) [24].

CONCLUSIONS

Multiple sclerosis (MS), a demyelinating disorder which mainly affects young adults, is uncommon under the age of 18 years. In the paediatric population, the course of the disease is characterised by high neuroinflammatory activity and frequent relapses [20]. The treatment process of POMS seems to be more challenging. The progress that has been made in the therapy of MS in recent years has significantly influenced the variety of therapies available for adult patients. Not all drugs are registered for underage patients, which makes it difficult or impossible to access the best treatment for the patient.

JIA, the most commonly diagnosed arthropathy in the paediatric population, is quite well known. As the condition progresses, inflammatory changes spreading into other musculo-skeletal structures. Pharmacotherapy of JIA has many possibilities, from basic anti-inflammatory steroids and non-steroid drugs, to highly specific monoclonal antibodies [25]. Choosing a personalised therapy is a key point for achieving therapeutic success.

Combined therapy of two autoimmune diseases should be an appropriate treatment for both of these conditions simultaneously, but also might have a high risk of side-effects. The use of immunosuppressive drugs may increase the risk of infectious complications; therefore, close monitoring of the patient's health during regular medical check-ups and laboratory tests is necessary during their use.

Both DMF and ofatumumab have been consecutively used with success in a patient with co-existing MS and JIA treated concomitantly with secukinumab. However, more evidence of the safety of such therapy is needed.

Informed consent. Informed consent was been obtained from the patient in the Case Report for publication of his case in the *Journal of Pre-Clinical and Clinical Research*.

REFERENCES

1. Landry RL, Embers ME. The Probable Infectious Origin of Multiple Sclerosis. NeuroSci. 2023;4(3):211–234. https://doi.org/10.3390/neurosci4030019
2. Hennet T, Borsig L. Breastfed at Tiffany's. Trends Biochem Sci. 2016;41(6):508–518. https://doi.org/10.1016/j.tibs.2016.02.008
3. De Silvestri A, Capittini C, Mallucci G, et al. The Involvement of HLA Class II Alleles in Multiple Sclerosis: A Systematic Review with Meta-analysis. Dis Markers. 2019;2019:1409069. https://doi.org/10.1155/2019/1409069

4. Cimaz R. Systemic-onset juvenile idiopathic arthritis. Autoimmun Rev. 2016;15(9):931–934. https://doi.org/10.1016/j.autrev.2016.07.004
5. Brenton JN, Kammeyer R, Gluck L, et al. Multiple Sclerosis in Children: Current and Emerging Concepts. Semin Neurol. 2020;40(2):192–200. https://doi.org/10.1055/s-0040-1703000
6. Jakimovski D, Awan S, Eckert SP, et al. Multiple Sclerosis in Children: Differential Diagnosis, Prognosis, and Disease-Modifying Treatment. CNS Drugs. 2022;36(1):45–59. https://doi.org/10.1007/s40263-021-00887-w
7. Steinborn B. Stwardnienie rozsiane w wieku rozwojowym. In: Losy J, editor. Stwardnienie rozsiane. 2nd ed. Lublin; 2019. p. 233–255. Polish.
8. Chighizola CB, Ferrito M, Marelli L, et al. Juvenile Idiopathic Arthritis, Uveitis and Multiple Sclerosis: Description of Two Patients and Literature Review. Biomedicines. 2022;10(8):2041. https://doi.org/10.3390/biomedicines10082041
9. Coşkun AN, Günbey C, Göçmen R, et al. Concurrence of juvenile idiopathic arthritis and primary demyelinating disease in a young child. Mult Scler Relat Disord. 2019;27:20–22. https://doi.org/10.1016/j.msard.2018.10.002
10. Puszczewicz MJ, Tuchocka-Piotrowska A, Majewski D, et al. Przypadek współwystępowania młodzieńczego idiopatycznego zapalenia stawów i stwardnienia rozsianego. Ann Acad Med Stetin. 2006;52 Suppl 2:85–88. Polish.
11. Krawiec P, Batko B. Zastosowanie sekukinumabu w leczeniu pacjentów z łuszczycowym zapaleniem stawów i chorobami współistniejącymi. Forum Reumatol 2020;6(2):85–90. https://doi.org/10.5603/FR.2020.0011
12. Baraliakos X, Gossec L, Pournara E, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: results from the double-blind, randomised, phase 3 MAXIMISE trial. Ann Rheum Dis. 2021;80(5):582–590. https://doi.org/10.1136/annrheumdis-2020-218808
13. Blair HA. Secukinumab: A Review in Psoriatic Arthritis. Drugs. 2021;81(4):483–494. Erratum in: Drugs. 2021;81(6):735. https://doi.org/10.1007/s40265-021-01476-3
14. Eshwar V, Kamath A, Shastry R, et al. A Review of the Safety of Interleukin-17A Inhibitor Secukinumab. Pharmaceuticals (Basel). 2022;15(11):1365. https://doi.org/10.3390/ph15111365
15. Vermersch P, Scaramozza M, Levin S, et al. Effect of Dimethyl Fumarate vs Interferon β-1a in Patients With Pediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial. JAMA Netw Open. 2022;5(9):e2230439. https://doi.org/10.1001/jamanetworkopen.2022.30439
16. Saidu NEB, Kavian N, Leroy K, et al. Dimethyl fumarate, a two-edged drug: Current status and future directions. Med Res Rev. 2019;39(5):1923–1952. https://doi.org/10.1002/med.21567
17. Dello Russo C, Scott KA, Pirmohamed M. Dimethyl fumarate induced lymphopenia in multiple sclerosis: A review of the literature. Pharmacol Ther. 2021;219:107710. https://doi.org/10.1016/j.pharmthera.2020.107710
18. Liang G, Chai J, Ng HS, et al. Safety of dimethyl fumarate for multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord. 2020;46:102566. https://doi.org/10.1016/j.msard.2020.102566
19. Di Tullio F, Odorici G, Lasagni C, et al. Combination treatment with secukinumab and dimethyl fumarate in a patient with psoriasis and recent diagnosis of multiple sclerosis. Dermatol Ther. 2020;33(6):e13943. https://doi.org/10.1111/dth.13943
20. Vitale C, Falchi L, Ciccone M, et al. Ofatumumab is safe and effective as front-line treatment in older patients with chronic lymphocytic leukemia and severe co-morbidities, including other malignancies. J Geriatr Oncol. 2020;11(1):19–23. https://doi.org/10.1016/j.jgo.2019.04.002
21. Bar-Or A, Wiendl H, Montalban X, et al. Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis: APLIOS, a randomized phase-2 study. Mult Scler. 2022;28(6):910–924. https://doi.org/10.1177/13524585211044479
22. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med. 2020;383(6):546–557. https://doi.org/10.1056/NEJMoa1917246
23. Kang C, Blair HA. Ofatumumab: A Review in Relapsing Forms of Multiple Sclerosis. Drugs. 2022;82(1):55–62. Erratum in Drugs. 2022;82(1):63. https://doi.org/10.1007/s40265-021-01650-7
24. Novartis Pharmaceuticals Corporation. KESIMPTA® (ofatumumab) injection, for subcutaneous use: US prescribing information. https://www.hcp.novartis.com/products/kesimpta/rms. (accessed 2021.11.16).
25. Zaripova LN, Midgley A, Christmas SE, et al. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol Online J. 2021;19(1):135. https://doi.org/10.1186/s12969-021-00629-8