


CLINICAL CASE

Sustained drug-free remission in rheumatoid arthritis associated with diffuse large B-cell lymphoma following tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy using zamtocabtagene autoleucel

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ABSTRACT

We report the case of long-term persisting rheumatoid arthritis (RA), treated with CD20-CD19 CAR-T when it became associated with diffuse large B cell lymphoma (DLBCL), resulting in a sustained drug-free remission of the preceding RA, as well as of the subsequent DLBCL that formed the indication of the CAR-T therapy using zamtocabtagene autoleucel, with a 1-year follow-up. According to our best knowledge, this is the first published clinical case report of long-term persisting RA treated with CAR-T cell therapy.

INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic autoimmune disease that is associated with systemic complications (eg, cardiovascular, lung and central nervous system manifestations) in addition to joint involvement. The synovial inflammation of various joints, typically joints of the hands and feet, leads to bone erosions, cartilage destruction and joint deformities.

The pathogenesis of RA is largely unknown; genetic and environmental factors have significant contributions; cigarette smoking is a strong predisposing factor. Both rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA) are unfavourable prognostic factors in RA. Although the current treatment strategy, especially the use of targeted synthetic and biological therapies, improved the outcome of the disease, many patients remain symptomatic and clinically active despite adequate treatment^{1 2} (difficult-to-treat-RA

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rheumatoid arthritis (RA) is a B cell-driven systemic autoimmune disease characterised by synovial inflammation of joints leading to destructive complications, of which long-term persisting and difficult-to-treat forms (D2T-RA) can lead to decades-long treatment beside remaining clinically active and symptomatic, for which B cell-depleting chimeric antigen receptor T cell (CAR-T) treatment, that is applied already for the treatment of B cell malignancies, may be a treatment option.

WHAT THIS STUDY ADDS

⇒ This is the first published case report of long-term persisting RA treated with CAR-T cell treatment after its association with diffuse large B cell lymphoma (DLBCL), showing the effectivity of this treatment against both RA and DLBCL with a 1-year follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our present case indicates that zamtocabtagene autoleucel could be an alternative efficacious curative treatment option for long-term persisting RA.

(D2T-RA)), and drug-free remission remains exceptionally rare,³ especially in the presence of bad prognostic factors.

Diffuse large B cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin's lymphoma (NHL), comprising 30%–40% of all NHL cases, originating from lymph nodes and presenting with lymphadenopathy and can be accompanied by systemic inflammatory symptoms (ie, B symptoms: fever, night



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RA / DLBCL TREATMENT SUMMARY

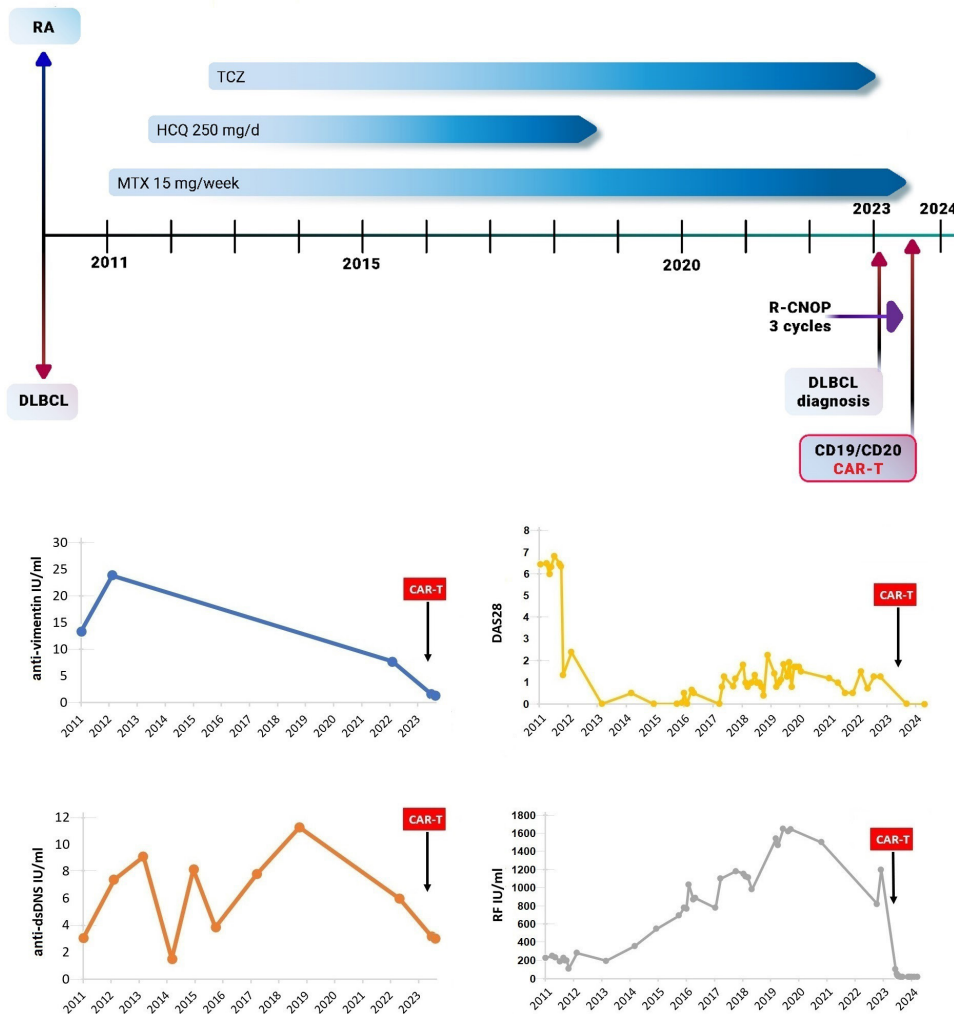


Figure 1 Patient with long-term persisting RA, associated with new-onset DLBCL treated by CAR-T. This panel summarises the treatments given for RA preceding DLBCL and subsequent treatments for DLBCL, as well as RA disease activity score DAS28, anti-vimentin and anti-double-stranded DNA antibody (anti-dsDNS) levels, and Rheumatoid Factor (RF) levels. CAR-T: chimeric antigen receptor T cell; DLBCL: diffuse large B cell lymphoma; R-CNOP: rituximab, cyclophosphamide, mitoxantrone, vincristine and prednisolone; RA: rheumatoid arthritis.

sweat and weight loss) and tissue infiltrations that can cause organ obstruction and compression symptoms, with a rapid growth rate and rapidly fatal if untreated. Its current standard first-line treatment is cyclophosphamide, adriablastine, vincristine and prednisolone combination chemotherapy since the 1970s, and with added rituximab since the 2000s (R-CHOP) or its analogue variants. Especially patients not responding or relapsing after first-line treatment (relapsed/refractory (r/r) DLBCL) bear a challenge to the treating physician. The treatment of r/r DLBCL has recently undergone a revolution with the availability of chimeric antigen receptor T cell (CAR-T) treatments.⁴

CASE REPORT

We report here the use of autologous CD20-CD19 CAR-T cells in the treatment of r/r DLBCL that was associated with preceding and long-term persisting RA, resulting

in a sustained drug-free remission of RA, as well as of DLBCL that formed the indication of CAR-T treatment.

A 73-year-old male patient developed joint pain in 2010; 1 year later, the diagnosis of RA was established. The patient was and is still a heavy smoker up to August 2024 with 50 pack-years, currently still smoking one pack daily, and it is to be noted that in addition to its known association with RA, some studies also suggested a connection between heavy smoking and lymphoma.⁵ The patient had a highly active disease (Disease Activity Score in 28 joints (DAS28) at diagnosis: 6.43), associated with low titre ACPA positivity (31 IU/mL) and high titre RF positivity (250 IU/mL). Low-dose glucocorticoid and 15 mg/week methotrexate (MTX) were initiated in 2011, but no higher doses were possible due to increased liver enzyme levels. Hydroxychloroquine (HCQ) was also started (250 mg/day) due to high clinical disease activity. As clinical disease activity remained still high, thereafter

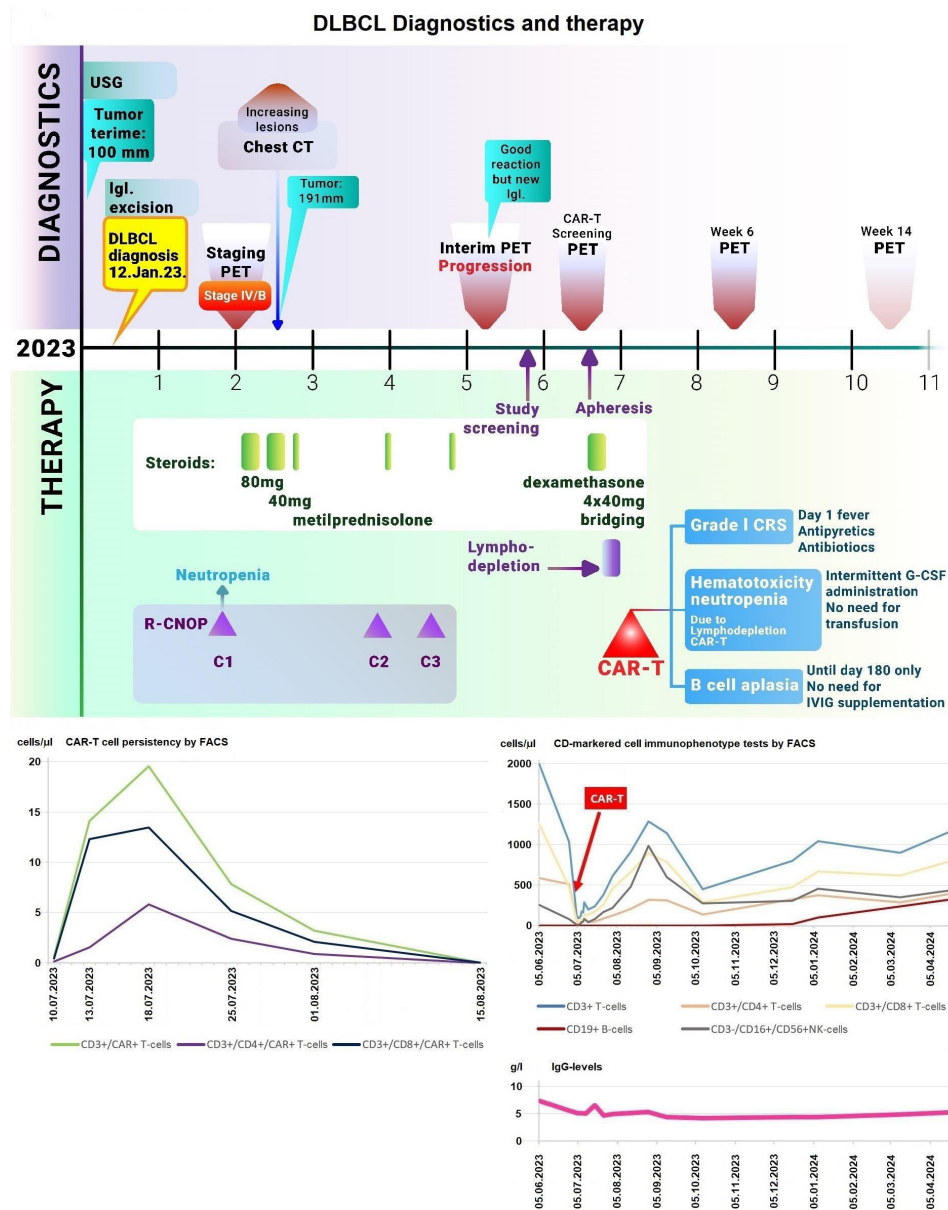


Figure 2 Upper graph summarises the main diagnostics and the therapy administered for DLBCL. The lower left graph shows the circulating CAR-T cell numbers following CAR-T administration. The right middle graph shows representative flow cytometric analysis results of circulating CD-marked cell numbers. The right lower graph shows the IgG levels. CAR-T: chimeric antigen receptor T cell; DLBCL: diffuse large B cell lymphoma; PET: positron emission tomography; R-CNOP: rituximab, cyclophosphamide, mitoxantrone, vincristine and prednisolone.

the interleukin-6 inhibitor tocilizumab (TCZ) was started intravenously with the general dose of 8 mg/kg every 4 weeks (a total of 560 mg). Glucocorticoid treatment was tapered and discontinued; the patient had low/moderate disease activity with MTX+HCQ+TCZ therapy between 2011 and 2018, when HCQ was discontinued due to the ophthalmologist's recommendation. The patient showed a good response to the applied therapy over time; however, the RF serum level continuously increased. In 2019, the RF level topped at 1645 IU/mL and remained constantly in that high range, accompanied with the fluctuating symptoms of RA and periods of severe pain. TCZ therapy was not switched due to patient preference in addition to the good clinical response.

In January 2023, a swollen cervical lymph node was observed and excised; histology confirmed Germinal Centre B cell-like-DLBCL,⁶ after which TCZ was stopped immediately, and the patient regularly visited the haematology department for tight control of DLBCL and discontinued rheumatology visits due to patient-related burden, while treatments for lymphoma were administered. Based on telemedicine, the patient had mild to moderate RA symptoms in this period. According to DLBCL staging examinations in February 2023, the initial disease stage was IV/B as per the Lugano classification system, with bulky right cervical lymphoid conglomerate, and rituximab, cyclophosphamide, mitoxantrone, vincristine and prednisolone (R-CNOP) chemoimmunotherapy protocol

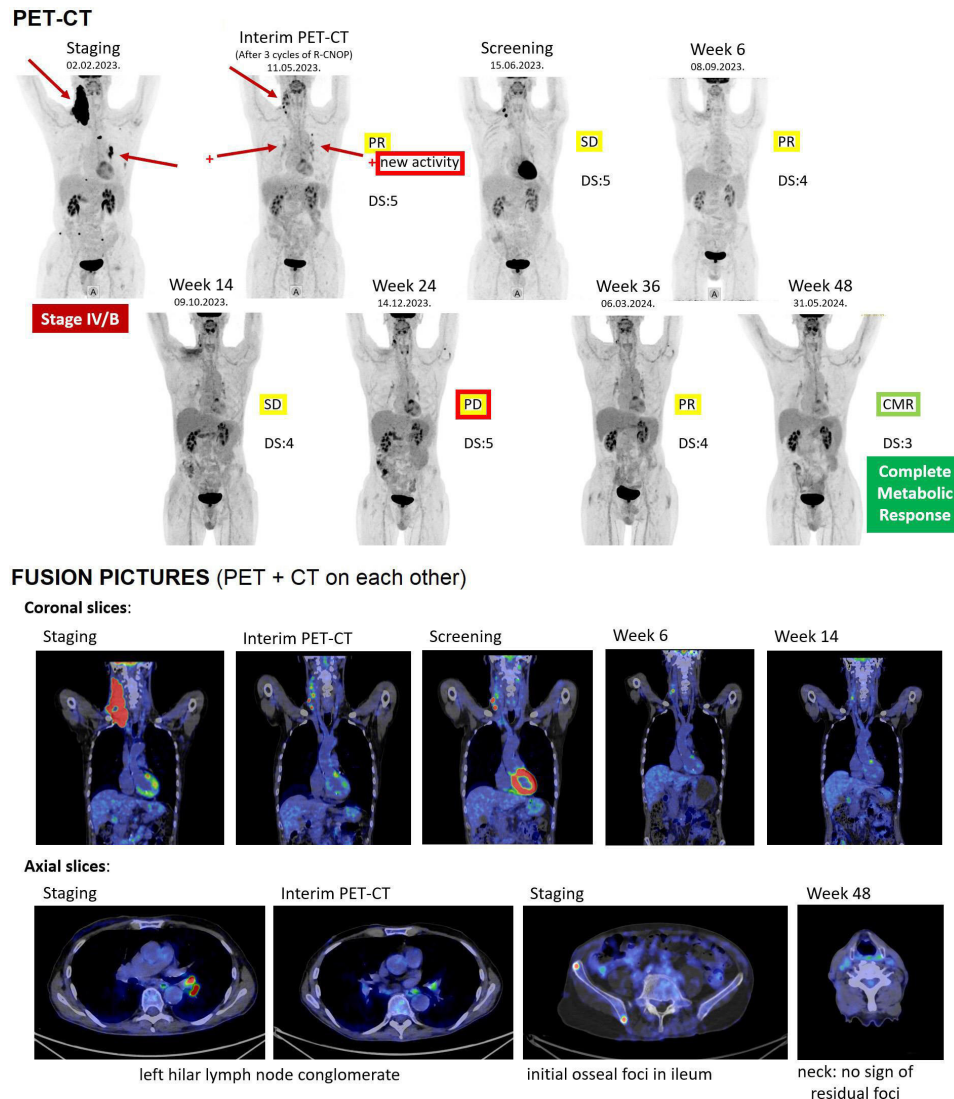


Figure 3 Pretreatment, post-R-CNOP and post-CAR-T PET-CT and CT scans. CAR-T: chimeric antigen receptor T cell; DS: Deauville Score; DLBCL: diffuse large B cell lymphoma; PD: progressive disease; PET: positron emission tomography; PR: partial response; R-CNOP: rituximab, cyclophosphamide, mitoxantrone, vincristine and prednisolone; SD: stable disease.

was initiated. After three cycles of treatment, interim positron emission tomography (PET)/CT restaging/analysis in May 2023 confirmed only a partial response, with strong suspicion of new mediastinal disease activity, due to which the patient was considered refractory to the applied treatment.

As a consequence, the patient was considered for second-line B cell depleting CAR-T treatment and was screened subsequently on 25 May 2023 in a pivotal phase II randomised, multicentre, open-label clinical trial (official short title: DALY 2-EU; original long title: A pivotal phase II randomised, multicentre, open-label study to evaluate the efficacy and safety of MB-CART2019.1 compared with standard of care therapy in participants with r/r DLBCL, who are not eligible for high-dose chemotherapy and autologous stem cell transplantation; EudraCT number: 2020-003908-14; sponsored by Miltenyi Biomedicine GmbH, Bergisch Gladbach,

Germany.⁷ MTX treatment of RA was discontinued after the screening visit for CAR-T treatment.

CD3+ cells were collected on 19 June 2023 by autologous fresh leukapheresis, from which tandem CD20-CD19-directed non-cryopreserved CAR-T cells (zamtocabtagene autoleucel, zamto-cel)⁸ were generated in Good Manufacturing Practice facility in the closed automated CliniMACS Prodigy system by transducing the autologous T-lymphocytes retrovirally with a CAR-containing intracellular CD3 ζ signalling domain and a 4-1BB co-stimulatory domain with a CD8 transmembrane domain. Manufacturing took 12 days, with an additional 2 days for leukapheresis transport and 1 day for fresh non-cryopreserved CAR-T transport, resulting in an overall 15-day vein-to-vein time, during which dexamethasone bridging therapy was applied. After conditioning lymphodepletion with fludarabine

and cyclophosphamide and transfusion of the manufactured fresh CAR-T cells were administered on day 0 (4 July 2023).

There was no severely immunocompromised state at the time of inclusion, no liver dysfunction presented, and there was no known history or presence of autoimmune central nervous system disease. CD19+ and CD20+ B cells were not detectable after the CAR-T treatment. After the administration of the CAR-T cell infusion, grade I cytokine release syndrome occurred, which was successfully treated with antipyretics. No immune effector cell-associated neurotoxicity syndrome, infection or tumour lysis syndrome was detectable. At haematological control on 25 July 2023, only a 1×1.5 cm long cervical lymph node was detectable by physical examination, and the patient had no complaints related to lymphoma.

Deep B cell aplasia developed and lasted until the day of +180 with only a mild decrease of IgG levels, not falling below 4.8 g/L, without the need for immunoglobulin replacement, indicating retained humoral immune memory and plasma cell functions. In response to recurrent neutropenia after the CAR-T cell therapy, the patient needed intermittent filgrastim injection until December 2023.

After the CAR-T treatment, CAR-T expansion was confirmed by flow cytometry (FC), followed by the consolidation phase. CAR-T cells were detected by FC between 10 July 2023 and 15 August 2023. A rise and subsequent decrease in white blood cell count also followed, also confirmed by FC immunophenotyping to different CD-marked cell subtypes (figure 1). Presently, no full set of detailed, specific laboratory analytics can be disclosed as the patient is still participating in the ongoing clinical study.

Subsequent rheumatology controls after the CAR-T therapy, from 26 July 2023, confirmed the patient staying in complete drug-free clinical remission of RA, which still lasts without interruption by 1-year follow-up of CAR-T treatment, resulting in a significant improvement of quality of life for the patient. The RF level showed a sharp decrease, from 1200 IU/mL right before diagnosis of DLBCL to 48 IU/mL after 3 weeks following CAR-T administration, further decreasing to around 13 IU/mL in upcoming months where it stagnates permanently (figure 2), in addition to low ACPA levels (indicating immunological remission as well). DLBCL remained in partial response (PR)/stable disease (SD) at radiology PET/CT controls, except at week 24, when the possibility of mild progressive disease (PD) was raised, which remained, however, unconfirmed by week 36 control that showed again PR, while finally, radiology control at week 48 demonstrated complete metabolic response (figure 3).

DISCUSSION

According to our best knowledge, this is the first published case report of long-term persisting RA treated with CAR-T cell therapy.^{9 10} Reaching its 1-year follow-up, RA remains in complete drug-free remission, which is exceptionally rare with the current standard protocol.¹⁻³ DLBCL, that formed the indication for CAR-T application, also did

and does not require further treatment, only close monitoring. It is known that chemotherapy for lymphoma can temporarily alleviate RA symptoms¹¹ and the applied treatment containing rituximab and dexamethasone bridging probably also contributed to it; however, long-lasting drug-free remission was achieved after CAR-T therapy in this case. Also notable is that the increasing reappearance of B cells after day 180 did not result in the reappearance of RA or DLBCL, indicating that the new B cell population no longer contained the defective clones causing RA or DLBCL. Moreover, the mild PD reported at week 24, followed by PR and then CMR at subsequent controls, may indicate that even if circulating CAR-T cells could no longer be detected, they might have remained active in tissues, continuing to eliminate the remainder of the malignant disease. These results suggest that besides effectivity against DLBCL, bispecific tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy with zamto-cel might be a therapeutic option in long-term persisting and possibly other severe forms of RA, such as D2T-RA.¹² The therapy appears to be effective both in RA and DLBCL by the temporary elimination of the B cell line up to plasmablast state, including the malignant B cell clone as well as B cells participating in the maintenance of the autoimmune response.¹²

Our case has some limitations, as RA disease activity was measured in DAS-28 (calculated with erythrocyte sedimentation rate) instead of the Clinical Disease Activity Index score that would have been more appropriate to TCZ therapy.

In autoimmune diseases, the potential role of B cell depletion was recently raised by more publications,¹³⁻¹⁹ including RA,⁹ and similar efficacy was reported with CD19-directed cryopreserved CAR-T in a case of RA associated with myasthenia gravis.¹⁰ While presently no approved CAR-T therapy is indicated for them, the following have published results of successful experimental treatment with it besides the aforementioned ones: systemic lupus erythematosus,^{14 15} systemic sclerosis,¹⁷ antisynthetase syndrome¹³ and idiopathic inflammatory myositis,¹⁹ while more CAR-T trials are underway for further ones.²⁰

Well-designed clinical trials at specialised centres are needed to study the potential place of CAR-T therapy in the treatment of RA and other autoimmune diseases. Given the role of B cells in a variety of immune-mediated diseases, the findings of this case underline that CAR-T therapy with zamto-cel that targets B cells may have future applications in its treatment.

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Contributors Eliza Szabó participated with graphic design. Péter Tóth participated with Excel data processing and study logistic system design. DS prepared the first draft of the manuscript with the help of GN. AB, GN and GZ reviewed and corrected the manuscript. AB, LG, LG-K, GL, MP, MR, PR and GN provided the data and treated the patient. DS, PT, PvH, GZ, SH, TO and SM designed and organised the study. SM conceptualised the CAR-T construct and manufacturing platform. DS had access to and verified the data. AB, DS and GN interpreted the data. DS and GN, as guarantors, accept full responsibility for the work and conduct of the study, have access to the data and control the decision to publish.

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Competing interests DS, PT, PvH, GZ, SH, TO and SM are employees of Miltenyi Biomedicine GmbH. GN received speaker honoraria from Astra Zeneca, AbbVie, GSK, Lilly, Pfizer, MSD, Roche, Miltenyi, SOBI and Swixx.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Hungarian Medical Research Council's Ethics Committee for Clinical Pharmacology, Báthory u. 10., Budapest, Hungary, case file number BMEÜ2168-0/2022-EKL. EudraCT number: 2020-003908-14. Participants gave informed consent to participate in the study before taking part.

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