Platelet-Rich stroma from Crohn’s disease patients for treatment of perianal fistula shows a higher myeloid cell profile compared to non-IBD controls

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ABSTRACT

Background: New cell-based therapies are under investigation to improve perianal fistulizing Crohn’s disease (pCD) healing. Autologous stromal vascular fraction combined with platelet-rich plasma (referred to as platelet-rich stroma [PRS]) is a new adipose-derived stromal therapy. The effect of Crohn’s disease (CD) on adipose tissue, and adipose-derived therapies, is largely unknown. We characterized the cellular composition of subcutaneous lipoaspirate and PRS of pCD patients and non-Inflammatory Bowel Disease (IBD) controls.

Methods: Consecutive pCD patients (>18 years) and non-IBD controls, who underwent liposuction for the purpose of autologous PRS therapy, were included (October 2020 and March 2021). Mechanically fractionated lipoaspirate and the combined PRS product were analyzed for cell surface marker expression using fluorescence-activated cell sorting analysis.

Results: Twenty-three patients (37.8 [IQR 30.7–45.0] years; 9 [39.1 %] male; 11CD patients) were included. Similar total number of cells were found in CD and non-IBD lipoaspirate (CD 8.23 ± 1.62*10^5 cells/mL versus non-IBD 12.20 ± 3.39*10^5). Presence of stromal cells, endothelial like cells, immune cells, T-cells, myeloid cells and M2/M1 macrophage ratio were similar in CD and non-IBD lipoaspirate. In PRS samples, more cells/mL were seen in CD patients (P = 0.030). Myeloid cells were more abundant in CD PRS samples (P = 0.007), and appeared to have a higher regulatory M2/M1 ratio. Interdonor variation was observed between lipoaspirate and PRS samples.

Conclusions: The composition of CD and non-IBD lipoaspirate were found to be similar and interdonor variation was observed. However, PRS from CD patients showed more myeloid cells with a regulatory phenotype. Crohn’s disease does not appear to alter the immunological composition of adipose-derived products.

1. Introduction

Perianal fistulizing Crohn’s disease (pCD) affects up to 30 % of Crohn’s disease (CD) patients (Schwartz et al., 2019). pCD is associated with a significant morbidity, resulting in a reduced quality of life and increased health care costs (Aguilera-Castro et al., 2017; Panes et al., 2018). There is a high need for new therapies, since many pCD patients are refractory to conventional approaches (Nielsen et al., 2009).

Mesenchymal stromal cells (MSC), sometimes referred to as mesenchymal stem cells or just stem cells, can be obtained from various tissues, including adipose tissue, bone marrow and placenta. Over the past 15 years, MSC have been rising as a therapeutic tool in a range of diseases including perianal fistula due to their regenerative and immunomodulatory properties (Cheng et al., 2020; Franco et al., 2018; Wu et al., 2020; Puissant et al., 2005). Several trials evaluating the potential of these cells in the therapy of pCD are ongoing, mostly using those

Abbreviations: PRP, Platelet-rich Plasma; SVF, Stromal vascular fraction; PRS, Platelet-rich stroma; ADSC, Adipose-derived stromal cell.
obtained from the adipose tissue. Recent studies have examined the effect of autologous stromal vascular fraction (SVF) as a low-cost alternative to allogenic adipose derived stromal cells (ADSCs) (Guo et al., 2016). SVF contains a heterogeneous cell population including ADSCs, pericytes, leukocytes, endothelial cells, and smooth muscle cells and is thought to have immunomodulatory and wound healing properties (Bourin et al., 2013). Advantages of autologous SVF are the minimal invasive harvest procedure, great availability of tissue supply and a short procedure time which allows for intraoperative preparation during fistula surgery without the risk of immune rejection (Van Dongen et al., 2019; Lightner et al., 2018; Nguyen et al., 2016; Conde-Green et al., 2016).

Recently, the landmark trial by Panes et al. demonstrated that injection of ex vivo expanded allogenic ADSCs as adjunct to surgical closure of the internal opening results in a remission rate of 52 %, compared to 36 % with placebo (Panes et al., 2018). This suggests that additional enhancement of local wound healing, induced by cell therapy, is needed (Sun et al., 2019). It is advocated that the regenerative properties are found not only in ADSCs, but also in the heterogeneous cell population of the lipospirate they are derived from, i.e. the SVF (Nguyen et al., 2016). Recent studies have shown that SVF combined with platelet-rich plasma (PRP), together referred to as platelet-rich stroma (PRS) (Deijl et al., 2020), as an adjunct to perianal fistula surgery is safe and well-tolerated in cryptoglandular fistulas and has shown promising results (Schouten et al., 2021; Serrero et al., 2019).

The development of ADSC therapies has raised the question as to whether CD adipose tissue is safe for autologous usage since adipose tissue is regarded as an active endocrine and immunologic organ. Alterations in adipose tissue in CD have been described, both in terms of tissue hypertrophy (creeping fat) and in cellular phenotype (Serena et al., 2017; Kredel et al., 2013; van der Meer et al., 2020; Ha et al., 2020; Peyrin-Biroulet et al., 2012). This study was conducted to better understand the cell populations present in lipospirates in order to improve knowledge on the use of cell-based therapy in CD patients in the future. To this end, this study aimed to perform an exploratory characterization of the cellular composition of subcutaneous lipospirate and PRS products in pCD patients and non-IBD controls.

2. Materials & methods

2.1. Study design

Consecutive pCD patients who underwent liposuction for the purpose of SVF with PRP procedure were included between October 2020 and March 2021. Patients were considered eligible when aged 18 years or older with confirmed CD diagnosis at time of surgery. Non-IBD controls were defined as patients with cryptoglandular perianal fistula without any clinical, endoscopic and/or histological sign of IBD. Exclusion criteria were active proctitis, presence of associated pelvic abscess(es), immune compromised status, hematological disorders, coagulation disorders or any oncological event in the past five years.

2.2. Endpoints

The primary endpoint was difference in presence of immune cell populations in CD patients compared to non-IBD controls in the lipospirate. Secondary endpoints included absolute cell counts, type of immune cells, presence of stromal cells and endothelial cells in lipospirate and combined PRS samples from CD patients compared to non-IBD controls.

2.3. Sample collection

All patients undergoing SVF with PRP surgery were operated by two trained colorectal surgeons (OR, CW). All patients underwent the same standard surgical protocol for the preparation of SVF and PRP (Deijl et al., 2020). In total, 30 mL of lipospirate was harvested during liposuction. Bilateral flanks served as the donor site for most patients, the abdomen was used as the donor site in two non-IBD patients with rectovaginal fistula due to positioning of the patient. Lipospirate was centrifuged (2,500 rpm, five minutes) and decanted, removing the oil and infiltration fluid fractions. Mechanical fractionation of cellular components was performed by passing the lipospirate forward and back thirty times through a disposable fractionator (01.4 μm, luer-to-luer transfer, Tulip). After mechanical fractionation, samples were centrifuged (2,500 rpm, five minutes) after which the upper oily phase was removed, leaving approximating 1 mL SVF. Simultaneously, 15 mL of whole blood was centrifuged (1,500 rpm, four minutes) after which 4–5 mL PRP was obtained from the upper layer (plasma). A total of ± 5 mL PRP and 1 mL SVF was combined to form PRS. PRS was injected through the curated fistula approximately within 2 mm around the internal fistula opening and into all quadrants of the fistula tract wall (Deijl et al., 2020). Samples were collected based on the availability of excess material to not interfere with the procedure. Excess samples of before and after mechanical fractionation and, in a subset of patients based on availability, PRP and PRS samples (PRP n = 8, PRS n = 11, Figure S1) were collected. All samples were immediately transferred on wet ice and processed at the Tygert Institute. Samples taken before and after mechanical fractionation were analyzed by flow cytometry (Figure S2). Baseline characteristics were collected at a standardized preoperative visit and included age, sex, previous fistula treatments including CD medication, medical history and smoking.

2.4. Cell isolation

All samples were transferred in phosphate buffered saline (PBS), 1 % Bovine Serum Albumin (BSA) (A3299-50ML; Sigma-Aldrich, St. Louis, MO), 1 % Fetal Calf Serum (FCS)/5mM ethylenediaminetetraacetic acid (EDTA) (E7889-100ML; Sigma-Aldrich, St. Louis, MO). For fluorescence activated cell sorting (FACS) analysis, lipospirate samples were enzymatically dissociated in 0.1 % collagenase A (clone H330, Biolegend), anti-CD3-AF488 (clone OKT3, Biolegend), anti-CD14-PE/Cy7 (clone 61D3, eBioscience), anti-CD206-APC (Clone 19.2, BD Bioscience), anti-CD163-BV605 (Clone GHI/61, Biolegend), anti-HLA-DR-PE (Clone L234, Biolegend), anti-C6D9-PerCP/Cy5.5 (Clone FN50, Biolegend), anti-CD90-PE/Cy7 (Clone 5 E10, Biolegend) and anti-CD31-FITC (Clone WM59, Biolegend). 4′, 6-Diamidino-2-phenylindole-dihydrochloride (DAPI) (Serva) was used to identify living cells. Cells were stained with the antibody mix in 5 mM EDTA in PBS and incubated on ice and in the dark for 30 min. Cell surface marker expression was analyzed by flow cytometry using a FACS device (LSRFortessa, BD Biosciences, Franklin Lakes, New Jersey) with FlowJo software (version 10, Treestar Inc. Ashland, Oregon).

2.5. Flow cytometry

Enzymatically dissociated cells collected from lipospirate and PRS samples taken at the operating room were analyzed for cell surface marker expression using FACS analysis. Cells were labelled with the following anti-human monoclonal antibodies: anti-CD45-AF700 (clone H330, Biolegend), anti-CD3- AF488 (clone OKT3, Biolegend), anti-CD14-PE/Cy7 (clone 61D3, eBioscience), anti-CD206-APC (Clone 19.2, BD Bioscience), anti-CD163-BV605 (Clone GHI/61, Biolegend), anti-HLA-DR-PE (Clone L234, Biolegend), anti-CD69-PerCP/Cy5.5 (Clone FN50, Biolegend), anti-CD90-PE/Cy7 (Clone 5 E10, Biolegend) and anti-CD31-FITC (Clone WM59, Biolegend). 4′, 6-Diamidino-2-phenylindole-dihydrochloride (DAPI) (Serva) was used to identify living cells. Cells were stained with the antibody mix in 5 mM EDTA in PBS and incubated on ice and in the dark for 30 min. Cell surface marker expression was analyzed by flow cytometry using a FACS device (LSRFortessa, BD Biosciences, Franklin Lakes, New Jersey) with FlowJo software (version 10, Treestar Inc. Ashland, Oregon).

2.6. Fixation of cells

In a subset of patients (n = 3), PRS samples were immediately fixed at the operation room in 4 % formalin solution in PBS. The samples were embedded in paraffin, 4.5 μm sections were cut and hematoxylin and eosin (H&E) staining was performed.
2.7. Statistical analyses

For collected samples, absolute cell counts were calculated based on the number of cells present in the solution. Percentages of cells expressing a cell surface marker together with the cell count were used to calculate the number of cells /mL for each cell type. Categorical variables were described using median and interquartile range. Baseline characteristics were compared between CD patients and non-IBD controls using the chi-square test or Fisher’s exact test for categorical and the Mann-Whitney U test for continuous variables. Differences in cell surface marker expression were calculated with GraphPad, version 8.3.0 (GraphPad software Inc., Los Angeles).

2.8. Ethical consideration

This study was performed in accordance with the 2008 Declaration of Helsinki. This study was reviewed and approved by the Medical Ethical Committee at the Erasmus Medical Center Rotterdam (MEC-2020-0499). Written informed consent was obtained from all subjects before enrollment.

3. Results

3.1. Baseline characteristics

In total, 23 patients who underwent liposuction for the preparation of SVF and PRP were included, with a median age of 37.8 (IQR 30.7–45.0) years and of whom nine (39.1%) were male. Eleven CD patients were included and twelve patients were non-IBD controls with cryptoglandular fistula. The median duration of fistulizing disease was 2.4 (IQR 1.6–4.4) years. The median body mass index (BMI) was 26.2 (IQR 22.9–29.7) kg/m² in CD patients versus 30.5 (IQR 27.1–36.8) in non-IBD controls (P = 0.010). Baseline characteristics are reported in Table 1.

3.2. Presence of stromal and myeloid cell types in liposapirate is comparable between CD patients and non-IBD controls

Similar numbers of cells were found in CD patients and non-IBD controls in liposapirate after mechanical fractionation (CD: 8.23 ± 1.62*10⁶ cells/mL, non-IBD: 12.20 ± 3.39*10⁶, P = 0.304, Fig. 1A). Stromal cells were seen in both CD patients and non-IBD controls and their presence did not differ significantly between both groups (P = 0.738, Fig. 1B and C). Endothelial cells were present in both groups and did not differ in number (P = 0.907, Fig. 1C and Fig. S3b). Likewise, there were similar numbers of immune cells in both CD liposapirate and non-IBD controls (P = 0.704, Fig. 1C). No difference between the two groups was also shown in the percentages of live cells (Stromal cells: P = 0.553, Endothelial-like: P = 0.219, Myeloid cells: P = 0.749) (Fig. 1D). Immune cells consisted mainly of T lymphocytes (median % in CD cell count: 45.5 %, non-IBD controls: 36.4 %, P = 0.823), and myeloid cells (median % in CD cell count: 12.9 %, non-IBD controls: 18.3 %, P = 0.412, Fig. 1E). Composition of the different cell types comparing CD patients versus non-IBD-controls is shown in the pie chart (Fig. 1F). CD206 was used as a marker to distinguish between regulatory M2 (CD206⁺) and pro-inflammatory M1 (CD206⁻) macrophages. No differences in M2/M1 ratio were seen between CD and non-IBD liposapirate (P = 0.323, Fig. 1G and Fig. S3c). Interdonor variation was observed between liposapirate and PRS samples.

3.3. Abundance of myeloid cells in platelet-rich stromal fractions in Crohn’s disease patients

Next, we evaluated the cellular composition of the PRS fraction, the combined product of the SVF and the PRP. PRP samples contained immune cells, but no stromal cells (Fig. 2A). Within the immune cells of the PRP, T cells were most abundant. PRS, analyzed in a subset of patients, contained cells from both immune and stromal lineages as expected (example shown in Fig. 2C). Quantification of cell numbers by Coulter Counter showed more cells per mL in PRS from CD patients (2.06 ± 5.62*10⁵, P = 0.010, Fig. 2D). The number of platelets was not determined since the coulter counter only measures nucleated cells. In PRS samples, a trend towards a higher concentration of stromal cells per mL was observed in CD patients, however this did not reach statistical significance (P = 0.087, Fig. 2E). T cells did not differ in number (P = 0.234, Fig. 2E). For immune cells, a wide variation in cell count between patients was observed (P = 0.323, Fig. 2E). These differences were only seen in cells/mL and were not present in the percentages of live cells (stromal cells: P = 0.140, endothelial-like: P = 0.258, myeloid cells: P = 0.577) (Fig. 2F). T cells (median % in CD cell count: 48.6 %, non-IBD controls: 45.4 %) did not differ significantly between CD patients and non-IBD controls (P = 0.586; Fig. 2G), myeloid cells (median % in CD cell count: 12.9 %, non-IBD controls: 11.1 %) were more abundant in PRS samples from CD patients (P = 0.007, Fig. 2G). Composition of the different cell types in PRS comparing CD patients versus non-IBD-controls is shown in the pie chart (Fig. 1H). Further characterization of the myeloid cells showed a
Fig. 1. Ratio of different cell types in lipoaspirate is comparable between CD patients and non-IBD patients (A) Cells per mL lipoaspirate after mechanical fractionation in CD patients (n = 11) and non-IBD patients (n = 11). (B) Representative example of gating showing presence of CD45+ cells and CD90+ cells in a Crohn’s disease patient and non-IBD control. Shown as percentage of living single cells. (C) Live stromal cells (CD90+), immune (CD45+) and endothelial like cells (CD31+) in Crohn’s disease patients (n = 11) and non-IBD controls (n = 12). Shown as cells per mL. (D) Presence of stromal, endothelial-like and immune cell subsets shown as a percentage of the total living cells. (E) Presence of CD3 + T cells and CD14 + myeloid cell expression in live CD45+ immune cells lipoaspirate in Crohn (n = 11) and non-IBD controls (n = 12). Shown as cells per mL. (F) Pie chart showing the distribution in cell composition of all gated cells. (G) Ratio of CD206+ /CD206− cells within the CD14+ myeloid compartment in Crohn’s disease patients and non-IBD controls. Dots represent individual patients, bars represent means, and error bars indicate SDs.
Fig. 2. Cell count in plasma rich stroma (PRS) (A) Representative example of gating showing presence of CD45^+ cells and CD90^+ cells in a PRP sample from a Crohn’s disease patient. (B) Dot plot showing presence of T cells and myeloid cells in PRP sample. (C) Representative example of gating showing presence of CD45^+ and CD90^+ cells in a PRS sample from a Crohn’s disease patient. (D) Cells per mL in PRS fraction from Crohn’s disease (n = 5) and non-IBD patients (n = 6). (E) Presence of stromal (CD90^+), immune (CD45^+), and endothelial like (CD31^+), cells in Crohn and non-IBD control. Shown as cells per mL. (F) Presence of stromal, endothelial-like and immune cell subsets shown as a percentage of the total living cells. (G) Presence of CD3^+ T-cells and CD14^+ myeloid cell expression in live CD45^+ immune cells in PRS in Crohn patients and non-IBD controls. Shown as cells per mL. (H) Pie chart showing the distribution in cell composition of all gated cells. (I) Ratio of CD206^+ /CD206^− cells within the CD14^+ myeloid compartment in PRS in Crohn’s disease patients and non-IBD controls. Dots represent individual patients, bars represent means, and error bars indicate SDs. Unpaired T-test, *p < 0.05, **p < 0.01.
A higher ratio of M2/M1, indicative of regulatory macrophages, in PRS samples from CD patients compared to non-IBD controls \( (P = 0.110, \text{Fig. 2I}) \).

### 3.4. Morphological characterization of the combination product platelet-rich stroma

Upon mixing the SVF with PRP, clotting was observed to varying degrees. To evaluate the nature of these aggregates, H&E staining of formalin fixed paraffin embedded (FFPE) sections of PRS was performed. These indicated that, even after mechanical fractionation, adipocytes were still present. Furthermore, this staining showed a high presence of nucleated non-adipocyte cells within aggregates of PRS from CD patients compared to non-IBD controls (Fig. 3A and B). This was in line with the higher cell count in PRS samples of CD patients.

### 4. Discussion

In this study, we demonstrated the presence of various cell populations in lipoaspirate and PRS that may be useful for fistula healing in pCD patients. Both the lipoaspirate and PRS seemed to be comparable between CD and the non-IBD patients, with regards to the presence of (stromal) cells and the cellular inflammatory profile, suggesting that this therapy could be suitable for patients with CD. Of note, characterization of the end product PRS revealed a higher number of total cells present in CD patients, with a more regulatory phenotype compared to non-IBD controls.

The characterization of the lipoaspirate showed similar cellular profiles between patients CD and non-IBD controls. Remarkably, relative low numbers of stromal cells were observed. Stromal cells play a pivotal role in tissue repair; however, there is an overall lack of consensus regarding the specific cell population and proportions of these cells needed to achieve wound healing (Guo et al., 2016). Furthermore, as indicated by Lightner et al. (Lightner, 2019), it is important to realize that SVF offers significant, but largely still unknown, potential to augment wound healing through the additional presence of vascular endothelial cells, leukocytes, and macrophages, embedded in a fibrovascular network (Lightner, 2019; Nunes et al., 2013).

The PRS samples contained a notable number of macrophages, which significantly differed between CD and non-IBD patients. While both sample groups display an overrepresentation of M1 macrophages in absolute numbers, the mechanism is more complex than one regulatory macrophage regulating one inflammatory macrophage. Therefore, the absolute ratio does not directly reflect an overall pro or anti-inflammatory state, but rather a relative presence of both. The increased ratio M2/M1 in the CD patients indicates is strongly suggestive for more regulatory activity than in the non-IBD samples. Macrophages play an important role in the wound healing response; pro-inflammatory macrophages initiate phagocytosis and removal of debris (Kim and Nair, 2019). In the following steps of wound healing, regulatory macrophages are important in tissue repair (Minutti et al., 2017; Murray et al., 2014). We were unable to confirm this due to low numbers of cases. We do know that anti-TNF therapy does not affect MSC function (Duijvestein et al., 2011). Another hypothesis is that the amount of CD45+CD14+ monocytes is increased in the plasma, and thus the PRP of CD patients, since anti-TNF therapy is known to increase the frequency of circulating monocytes (Nazareth et al., 2014). Future studies are needed to determine this.

A lower percentage of stromal and endothelial-like cells was found in the PRS samples compared to the lipoaspirate. During the preparation of the end product PRS, the lipoaspirate undergoes multiple preparation steps; including centrifuging, removing oily phases and addition of PRP. These processing steps might alter concentrations presence, such as

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**Fig. 3.** Hematoxylin and eosin (H&E) staining of formalin fixed paraffin embedded sections of platelet-rich stroma (A) H&E staining of platelet-rich stroma in Crohn’s disease patient (B) H&E staining of platelet-rich stroma in non-IBD control.
mean stromal cells (Fig. 2D).

Our study confirmed that interdonor variation in SVF exists, which might potentially result in variable therapeutic effects (van Dongen et al., 2019; Phinney, 2012). Several factors, including obesity, smoking (Buscetta et al., 2020), age, sex (McKinnirey et al., 2021) and external et al., 2019; Phinney, 2012). Several factors, including obesity, smoking inflammatory pathways including TNFα and IL-6 expression (Weisberg et al., 2003). Recent studies have shown a decrease in overall yield of nucleated cells in adipose tissue with increasing age (Choudhery et al., 2014; Alt et al., 2012) and a significant decrease in the proliferative and differentiation capacities of ASCs (Madonna et al., 2011). Our study was not powered to determine correlations between clinical factors and differences in cell counts. It is possible that the observed difference in age and BMI in our study alters the composition of SVF. However, we did not find a significance in correlation. From two donors, the liposuction material was taken from the abdomen, instead of the lateral flank. However, from literature it is known that location does not affect the viable cell numbers (Tsekouras et al., 2017). Further research is needed to determine the influence of clinical parameters of SVF composition and whether these factors should be considered in case of treatment failure.

To our knowledge, this study is the first to present an immunologic profile of cell types found within PRS products of adipose harvests in CD patients with perianal fistula. A few limitations need consideration.

First, this study was performed using residual material to limit the discomfort of the patient. Therefore, the PRS group contained less patients than the liposapirate group, as PRS could not be obtained from all patients. Since this is an exploratory study, the sample size was limited. Second, clinical outcomes were not considered in this study. Currently, multiple studies are being conducted to determine the clinical outcomes after autologous SVF with and without PRP (data in preparation) (Guillo et al., 2022). Third, no functional studies regarding the cell populations found were performed. A recent study (Barnhoorn et al., 2022), showed that cultured ADSCs were affected by cytokine mixes mimicking the internal CD fistula milieu, resulting in immunomodulatory properties of the MSC’s by producing cyclooxygenase-2, indoleamine 2,3-dioxigenase and TGF-β1. Based on the heterogeneity of the cell composition and its hypothetical working mechanism, functional test were considered not feasible in our study as they would require cell culture which would influence the phenotype of the stromal cell fraction. Last, there is a low consensus on the differentiation of ADSCs (Gimble et al., 2011), in our study stromal cells were defined based on CD90 expression. It is conceivable that the absence of one specific set of differentiation markers for e.g. stromal cells (Mildmay-White and Khan, 2017) could lead to an underestimation of the (stromal) cell populations in our study.

The use of autologous SVF combined with PRP for perianal fistulas in CD patients, could be a low-cost alternative for the use of allogenic ADSCs. The composition of CD and non-IBD subcutaneous lipoaspirate were found to be similar. Characterization of the adipose-derived PRS product showed more cells present in CD patients with myeloid cells with a more regulatory phenotype, which could have a more beneficial effect on fistula healing. New data on the clinical efficacy of SVF and PRS in patients with CD are awaited.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: C.J. Buskens has served on the advisory board for Johnson &Johnson energy devices; and has received consultancy fees and/or speaker’s honoraria from AbbVie, Boehringer Ingelheim, Janssen and Takeda, outside the submitted work. Annemarie C. de Vries has served on the advisory boards for Takeda, Janssen, Bristol Myers Squibb, Abbvie, Pfizer, Galapagos; and has received unrestricted research grants from Takeda, Janssen, Pfizer, outside the submitted work. C. Janneke van de Woude received grants and or fee for advisory boards and presentations from Pfizer, Abbvie, Celltrion, Falk Benelux, Takeda, Janssen, and Ferring, outside the submitted work. M.E. Wildenberg received research grants from Boehringer Ingelheim, Roche and GSK, outside the submitted work. Oddeke van Ruler has served as invited speaker for Janssen-Cilag; and has received a research grant from Takeda, outside the submitted work.

The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scr.2023.103039.

References


