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CLINICAL SCIENCE

Disease flares with baricitinib dose reductions and development of flare criteria in patients with CANDLE/PRAAS

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ABSTRACT

Objectives Patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS) respond to the janus kinase inhibitor 1/2 inhibition with baricitinib at exposures higher than in rheumatoid arthritis. Baricitinib dose reductions to minimise exposure triggered disease flares which we used to develop 'flare criteria'.

Methods Of 10 patients with CANDLE/PRAAS treated with baricitinib in an open-label expanded-access programme, baricitinib doses were reduced 14 times in 9 patients between April 2014 and December 2019. Retrospective data analysis of daily diary scores and laboratory markers collected before and after the dose reductions were used to develop 'clinical' and 'subclinical' flare criteria. Disease flare rates were compared among patients with <25% and >25% dose reductions and during study visits when patients received recommended 'optimized' baricitinib doses (high-dose visits) versus lower than recommended baricitinib doses (low-dose visits) using two-sided χ^2 tests.

Results In the 9/10 patients with CANDLE with dose reduction, 7/14 (50%) times the dose was reduced resulted in a disease flare. All four dose reductions of >25% triggered a disease flare ($p < 0.05$). Assessment of clinical and laboratory changes during disease flares allowed the development of disease flare criteria that were assessed during visits when patients received high or low doses of baricitinib. Disease flare criteria were reached during 43.14% of low-dose visits compared with 12.75% of high-dose visits ($p < 0.0001$). Addition of an interferon score as an additional flare criterion increased the sensitivity to detect disease flares.

Conclusion We observed disease flares and rebound inflammation with baricitinib dose reductions and proposed flare criteria that can assist in monitoring disease activity and in designing clinical studies in CANDLE/PRAAS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS) is a rare autoinflammatory interferonopathy.
⇒ A chronically elevated peripheral blood interferon (IFN) signature is a hallmark of incompletely treated CANDLE/PRAAS. Patients with CANDLE/PRAAS respond to the janus kinase inhibitor 1/2 inhibition with baricitinib at exposures higher than in rheumatoid arthritis.
⇒ Defining and validating disease outcomes and/or activity criteria in patients with ultrarare diseases remains an ongoing challenge.
⇒ Validated outcomes in autoinflammatory diseases have only been defined for interleukin-1 mediated autoinflammatory diseases.

WHAT THIS STUDY ADDS

⇒ We observed substantial rebound inflammation and disease flares with baricitinib dose reductions in patients with CANDLE/PRAAS that allowed us to develop disease flare criteria.
⇒ Baricitinib dose reductions of >25% resulted in disease flares in all patients, and reductions of <25% resulted in disease flares in 29% of the patients.
⇒ We developed (1) clinical flare criteria based on clinical and laboratory changes and (2) subclinical flare criteria based on laboratory changes only.
⇒ Flare rates using the proposed flare criteria were significantly higher during visits when patients received low doses of baricitinib than during visits when patients received higher doses of baricitinib.
⇒ The addition of the IFN score as flare criterion can be considered in patients who can normalise the IFN score.

INTRODUCTION

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS) is a rare autoinflammatory interferonopathy that is caused by loss-of-function mutations in genes that affect the 20S proteasome assembly and function. Patients respond to treatment with janus kinase inhibitors (JAKi), that reduce interferon (IFN) signalling associated with clinical improvement.[1–5] In an expanded access programme

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study highlights the need to monitor disease flares when baricitinib dose reductions are implemented and cautions against large reductions or drug discontinuation.
⇒ Our study provides a model for establishing and validating flare criteria using systematically collected data and addresses challenges faced when establishing outcomes in ultrarare inflammatory diseases.
⇒ Disease flare criteria aid in monitoring treatment responses and in designing clinical trials in patients with CANDLE/PRAAS in the future.

(NCT01724580), 50% of patients with CANDLE/PRAAS achieved lasting clinical remission on baricitinib with normalisation of the IFN response gene signature[1] but required higher exposure for optimal treatment compared with patients with rheumatoid arthritis.[3] The development of BK viral reactivation in urine, particularly the development of BK viraemia and BK nephropathy, as well as cytopenias observed at higher exposure required for treatment of CANDLE/PRAAS have led to close monitoring of BK viral load and attempts to minimise drug exposure in patients with controlled disease, with the goal to reduce baricitinib exposure/doses to the lowest dose needed to preserve disease control.

The development of postdose reduction disease flares presenting with fevers, rashes, musculoskeletal (MSK) symptoms, headaches and elevation of inflammatory markers in patients undergoing dose reductions allowed us to leverage these data to develop the proposed flare criteria for CANDLE/PRAAS to assist in monitoring disease activity and in the development of clinical trials in randomised withdrawal studies in CANDLE/PRAAS in the future.

METHODS

Patients

Patients with genetically confirmed CANDLE/PRAAS who received baricitinib in an open-label expanded access programme (NCT01724580) were included in this retrospective study.

Assessment of clinical flares post baricitinib dose reductions

We performed a retrospective data analysis by screening the clinical database (INFORM) for baricitinib dose reductions that occurred during the study period from October 2011 through December 2020 (online supplemental table 1). Medical records and daily diary scores (DDS) were reviewed to assess worsening of clinical symptoms suggestive of postdose reduction disease flares.[6] We extracted BK viral load in blood and urine before and after dose reductions. Clinical determination of disease flare was based on clinical judgement of the expert provider and included worsening of CANDLE/PRAAS associated clinical features (online supplemental table 2). We focused on acute changes in the context of a disease flare which do not include metabolic markers. The observed flare patterns in this study align with those previously reported in patients with active disease.[6 7]

Development of CANDLE/PRAAS disease flare criteria

Data were used from seven patients (P1, P3, P4, P5, P6, P7 and P10) to develop CANDLE/PRAAS disease flare criteria. The visit prior to dose reduction was used as reference visit to calculate postdose reduction changes. For the reference visit (see online supplemental table 3 for details), three patients (P4, P5 and P10) fulfilled remission criteria with 'no disease symptoms (DDS <0.15), normal C reactive protein (CRP) and off glucocorticoids' in accordance with the criteria established by Sanchez *et al*.[1] One patient P3 was considered to have minimal disease activity (DDS <0.15), normal CRP and glucocorticoids of <0.15 mg/kg/day. Two patients (P1 and P6) had stable/controlled disease on glucocorticoids ~0.3 mg/kg/day and one patient (P7) required 0.8 mg/kg/day of prednisone and had baricitinib withheld due to high BK viral load in blood (the subsequent visits were therefore not used in the confirmation phase).

Assessment of the CANDLE/PRAAS disease flare criteria in high-dose and low-dose baricitinib study visits

To assess the performance of the proposed flare criteria, we compared flare rates in six patients (P1, P3, P4, P5, P6 and P10) who were on low and high doses of baricitinib during the study. Four participants were excluded (P7: baricitinib was discontinued secondary to azotaemia; P2 and P9: did not have a low-dose period; and P8: did not have a dose reduction during the study period). Due to small sample size in this ultrarare disease, the same cohort was used for both development and assessment of the flare criteria.

Clinically 'effective baricitinib doses' were determined based on PK data (online supplemental table 4), that supported a currently recommended dosing regimen.[3] Patient visits on lower than 'effective doses' were categorised as 'low-dose' visits and those on equal or higher than 'effective doses' were categorised as 'high-dose' visits.

To assess the performance of the proposed flare criteria, we compared disease flare rates during high-dose visits and low-dose visits (online supplemental materials).

Statistical evaluation

Pairwise comparisons of DDS and laboratory biomarkers (reference vs flare visits) were performed via a two-sided Wilcoxon signed rank test. Time to flare was evaluated using a Cox proportional hazards model and data were displayed using Kaplan-Meier curves. The time to fulfilling the flare criteria was influenced by the timing of a postdose reduction blood draw. The maximal follow-up period consisted of 60 days. Flare rates were stratified by dose reductions of <25% and >25%. The proportion of disease flares was compared between the low-dose and the high-dose visits using a two-sided χ^2 test of homogeneity. Logistic regression with generalised estimating equations was performed to determine the odds of flare in low-dose versus high-dose visits adjusting for prednisone dosing. No multiple comparison adjustments were performed. All analyses were done in R V.4.0.4. Statistical significance was considered if $p < 0.05$.

RESULTS

Patients with CANDLE/PRAAS who had baricitinib dose reductions developed dose-dependent disease flares

Baseline demographics and clinical characteristics of 10 patients with CANDLE/PRAAS were previously described (online supplemental table 5).[1] The mean age at enrolment was 11.5 years (range 2.3–19.6).

During the study period (10/2011–12/2020), we identified 14 baricitinib dose reductions that occurred between April 2014 and December 2019 in 9 out of the 10 patients with CANDLE/PRAAS (figure 1). Following baricitinib dose reductions, we observed a concomitant decrease in BK viral load in blood and urine (online supplemental table 1); however, of the 14 dose

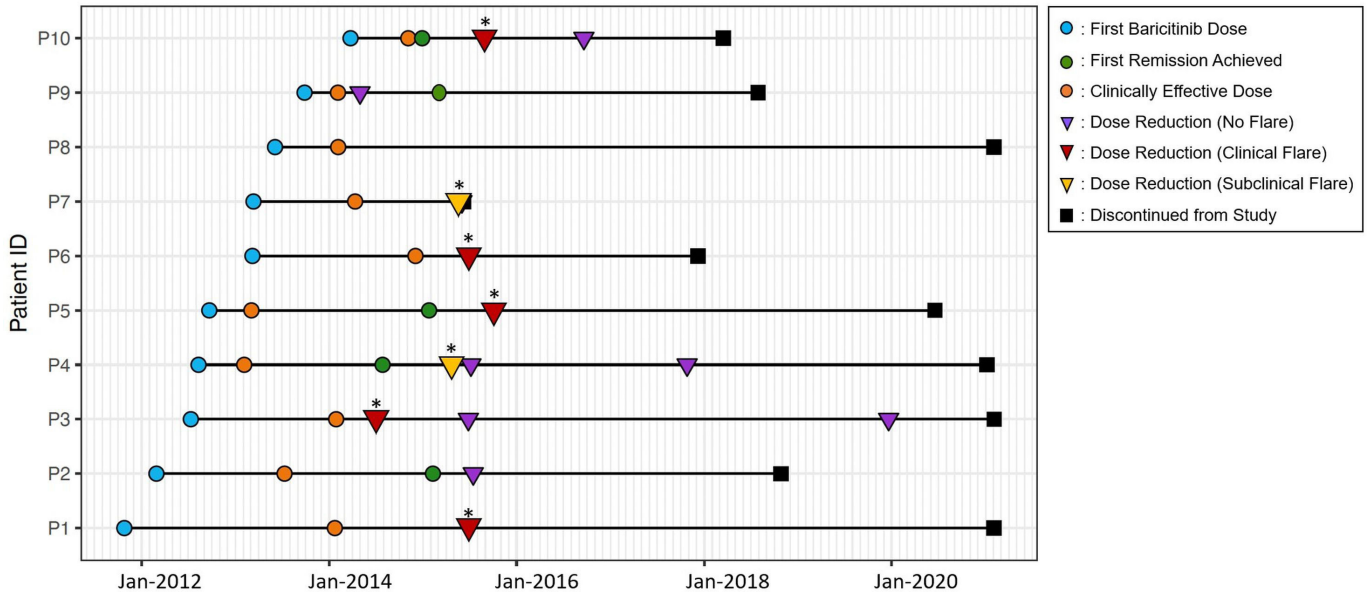

Figure 1 Timeline of baricitinib dose changes and development of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/ proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS) disease flare. Timeline of baricitinib initiation (blue circle), achieving the first remission (green circle), reaching clinically effective dose (orange circle), dose reduction not triggering a flare (purple triangle), dose reduction that triggered a clinical flare (red triangle), dose reduction that triggered a subclinical flare (yellow triangle) and study discontinuation (black square). Mean time to establish clinically effective dose was 1.06 years (±0.65 year) in 10 patients with CANDLE/PRAAS. Mean duration of baricitinib treatment was 6.3 years (±2.3 years). Of 10 patients, 9 had 14 baricitinib dose reductions. P8 did not have a dose reduction. Of 14 dose reductions, five (P1, P3, P5, P6 and P10) resulted in a clinical disease flare in five out of nine patients and two (P4 and P7) resulted in laboratory changes alone consistent with a disease flare with no clinical symptoms. *Indicates incidences of flare, clinical or subclinical.

reductions, 50% (7/14) resulted in flares. Five were associated with clinical symptoms and laboratory changes during the flare (P1, P3, P5, P6 and P10); and two flares were associated with laboratory changes (P4: CRP, absolute lymphocyte count (ALC) and white blood cell count (WBC) and P7: WBC, ALC and platelets (PLT)) without clinical symptoms. One patient (P7) with presumed BK nephropathy and elevated creatinine stopped baricitinib 8 days later. He developed macrophage activation syndrome (MAS), required treatment with pulse methylprednisolone and was ultimately treated with prednisolone 30 mg daily.

Flares were initially determined clinically based on the report of symptoms (including facial images of rash and periorbital oedema sent by email) that developed within days of the baricitinib dose reduction (not shown), physical examination (online supplemental table 2) and concomitant laboratory changes. We then assessed mean DDS changes before and after dose reductions (reference visit vs flare visit) to use a patient-reported measure to assess clinical disease activity. Available DDS (n=6) worsened between 15% to >500% (absolute change ranged between 0.055 and 0.314) (online supplemental table 2). Clinical flares postdose reduction were accompanied by changes in the six laboratory markers assessed, including CRP, erythrocyte sedimentation rate (ESR), WBC, haemoglobin (HGB), ALC and PLT (figure 2). One patient (P1) had an increase in the IFN score after dose reduction (online supplemental table 6a and online supplemental figure 1).

Establishing CANDLE/PRAAS disease flare criteria

To establish flare criteria, we systematically assessed the seven flares that were clinically determined, five were associated with clinical and laboratory features, and two with only laboratory changes. The changes in the laboratory criteria comparing the reference visit (online supplemental table 3) with the flare visit included increases in acute phase reactants; CRP (91% to >500%), ESR (39% to >500%) and the presence of cytopenias; a WBC decrease between 34% and 41%, an ALC decrease between 15% and 89%, a PLT count decrease between 24% and 47% and a HGB decrease between 1% and 14% (online supplemental table 6a). Of the five patients with worsening of clinical symptoms, one patient (P1) had a change in only one laboratory marker (23% decrease in ALC from baseline), and four (P3, P5, P6 and P10) had changes in four laboratory markers. Two patients who had laboratory changes with no clinical symptoms had changes in three laboratory markers (P4: CRP, WBC ALC; P7: WBC, PLT, ALC) (online supplemental table 6a). We defined two types of disease flare criteria (table 1):

(1) Clinical flare criteria with clinical symptoms that were either observed on physical exam or photos or a DDS change by >15% plus at least two laboratory changes, and (2) subclinical flare criteria defined by the absence of clinical disease features and at least three laboratory changes.

The flare criteria were then applied to all 14 dose reduction visits. Of the seven clinically determined flares, six fulfilled the flare criteria (four clinical flare visits (P3, P5, P6 and P10) and two subclinical flare visits (P4 and P7)); however, P1 did not fulfil the flare criteria. JAKi dose reductions that trigger flares depend on factors including the magnitude of the dose reduction, the actual baricitinib dose the patient received at the time of drug withdrawal and the level and duration of disease control at the time of dose reduction. In our patients, disease flares occurred in all four patients (100%) who had a dose reduction of >25%; two patients had clinical and two had subclinical flares. A dose reduction of <25% resulted in clinical flares in 2 (20%) of 10 dose reductions (figure 3 and online supplemental table 6a). We assessed P1 who had a clinically determined disease flare presenting with headaches, oral ulcers, MSK pain, fatigue but who did not fulfil the clinical disease flare criterion. He developed lymphopenia as the only laboratory flare criterion.

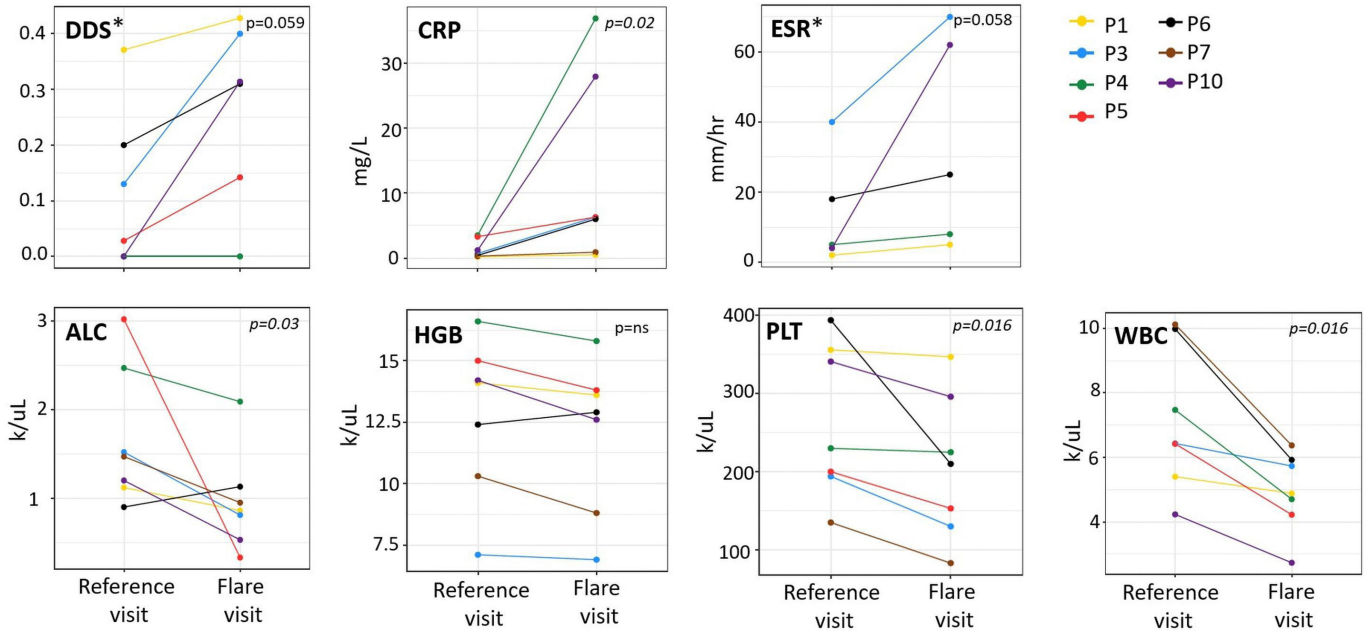

Figure 2 Acute clinical and laboratory biomarker changes with baricitinib dose reduction in seven patients judged to have a clinical or subclinical disease flare. This figure depicts comparison of the reference visit (=last visit before baricitinib dose reduction) with flare visit (=the first visit after baricitinib dose reduction) for DDS and the laboratory values for the patients who developed baricitinib dose reduction associated clinical and/or laboratory changes. Each parameter for each patient is graphed (see symbols used in upper right-hand corner of the graph for each patient). A two-sided non-parametric Wilcoxon signed rank test with uncorrected p values was used to underscore the descriptive representation. ALC, absolute lymphocyte count; CRP, C reactive protein; DDS, daily diary score; ESR, erythrocyte sedimentation rate; HGB, haemoglobin; PLT, platelets; WBC, white blood cell. *P7: DDS and ESR were not available for predose or postdose reduction visit or for both. P5: ESR was not available postdose reduction.

However, P1 had IFN scores assessed before and after the dose reduction, and the 25-gene IFN score increased from 31.21 to 236.29 (cut-off 44.2). We therefore subsequently evaluated the inclusion of the IFN score as an additional flare biomarker in a subanalysis by only including visits that had an IFN score assessed. The time from baricitinib dose reduction to fulfilling the proposed flare criteria required a blood draw postdose reduction and ranged from 1 to 55 days postdose reduction (mean 15.3 ±20.7 days). One patient had clinical symptoms with DDS changes several days after dose reduction; however, this patient did not have bloodwork done until 55 days after the dose reduction. To include laboratory changes, the maximum follow-up period consisted of 60 days. We included this patient since: (1) the patient had clinical changes after baricitinib dose reduction; (b) she did not have another baricitinib dose adjustment until blood work was done; and (c) we considered her clinical and laboratory changes consistent with the clinical changes post baricitinib dose reduction.

Table 1 Definition of clinical and subclinical CANDLE/PRAAS disease flare

Definition	Laboratory biomarkers*
Clinical flare criteria	CRP (≥ 40% increase)
A worsening in DDS† by a minimum of 15%	ESR (≥ 20% increase)
or the documentation of flare symptoms in the	WBC (≥ 20% decrease)
medical record	Platelets (≥ 20% decrease)
AND changes in two or more laboratory	ALC (≥ 15% decrease)
biomarkers	HGB (≥ 15% decrease)
Subclinical flare criteria	CRP (≥ 40% increase)
Less than 15% worsening in DDS† and/or no	ESR (≥ 20% increase)
flare symptoms on physician evaluation	WBC (≥ 20% decrease)
AND changes in three or more laboratory	Platelets (≥ 20% decrease)
biomarkers when compared with the reference	ALC (≥ 15% decrease)
visit	HGB (≥ 15% decrease)

*Acute change in laboratory biomarkers with disease flares compared with the reference visit (last visit with documented laboratory biomarkers prior to baricitinib dose reduction period). For inclusion as flare criterion, the change of CRP and/or ESR score must result in a clinically abnormal value and an increase of greater or equal to 20% must occur.
†Mean DDS for 7 days (ranges from 3 days before and after the visit).
ALC, absolute lymphocyte count; CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; CRP, C reactive protein; DDS, daily diary score; ESR, erythrocyte sedimentation rate; HGB, haemoglobin; WBC, white blood cell count.

Confirmation of the CANDLE/PRAAS flare criteria

To further evaluate the disease flare criteria, we hypothesised that patients on optimised doses of baricitinib would fulfil disease flare criteria less often than patients on low baricitinib doses. A total of 153 visits in 6 patients (P1, P3, P4, P5, P6 and P10) who had both high-dose and low-dose visits were identified; of those, 102 occurred on an optimal dose baricitinib (high-dose visits), and 51 on lower than currently recommended/optimised baricitinib doses (low-dose visits). Disease flare criteria were fulfilled in 43.14% of low-dose visits compared with 12.75% of high-dose visits ($p<0.0001$) (figure 4). The median baricitinib dose during the high-dose period compared with low-dose period was 9.00 (IQR 2.00) mg/day versus 6.00 (IQR 3.00) mg/day respectively, $p<0.0001$. The median prednisone equivalent dose was significantly lower in the high-dose period compared with low-dose period, 0.00 (IQR 0.136) mg/kg/day and 0.149 (IQR 0.13) mg/kg/day, respectively, $p<0.0001$ (online supplemental figure 2). Adjusting for prednisone equivalent dose, higher odds of a flare in the low-dose period when compared with the high-dose period were found ($p=0.03$) (online supplemental figure 3). Lastly, the IFN score was assessed in 29/56 (52%) low-dose visits and 79/102 (77%) high-dose visits. The median IFN score

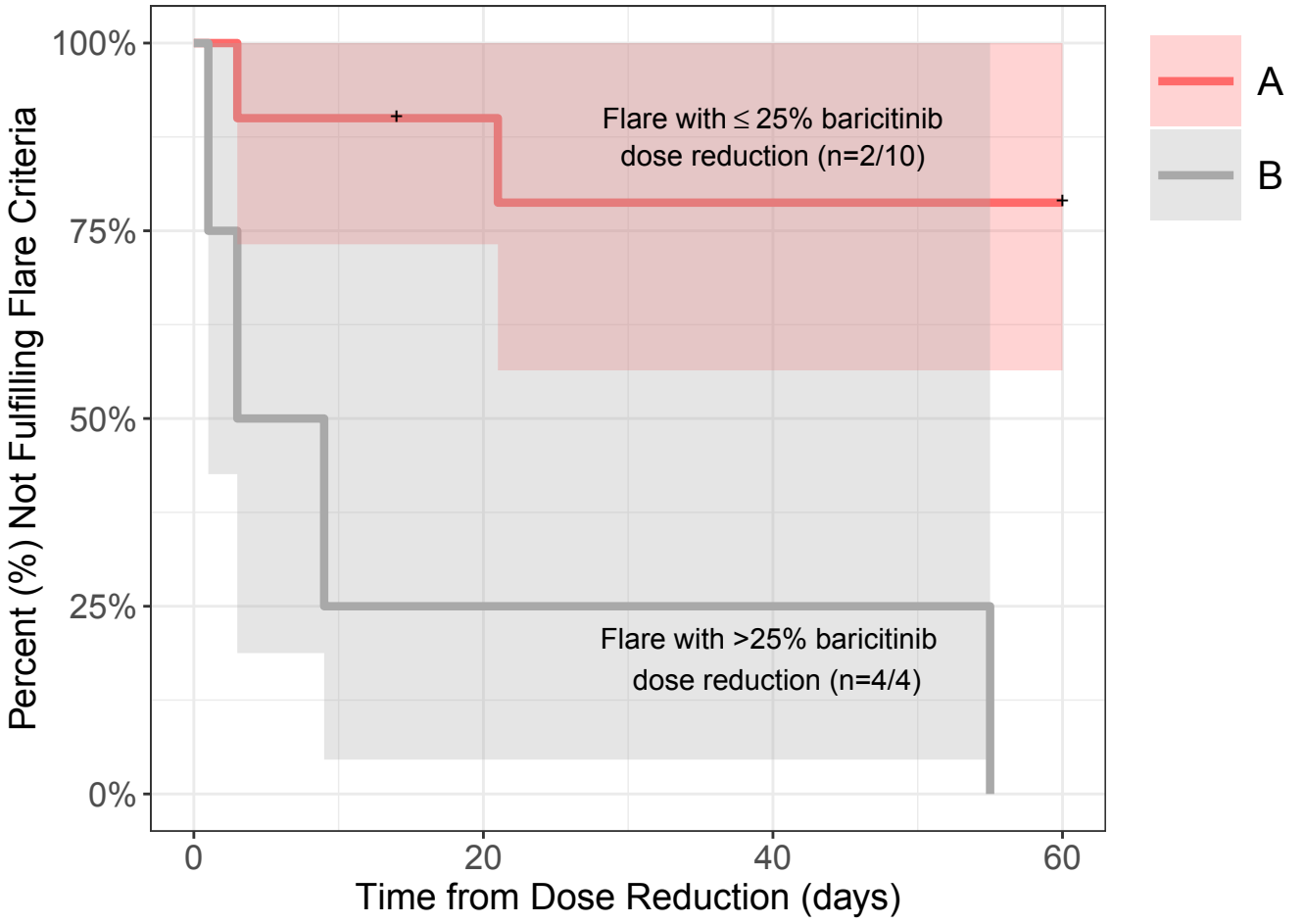

Figure 3 Time from baricitinib reduction to the fulfilment of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS) disease flare criteria (clinical and subclinical without interferon score). This Kaplan-Meier curve depicts the rate of disease flares (%) associated with baricitinib dose reductions in patients with CANDLE/PRAAS on y-axis, and time from dose reduction to flare in days on x-axis. Red line (group A) represents patient visits with a less than or equal to 25% baricitinib dose reduction (n=10) and the grey line (group B) represents occurrences of greater than 25% of baricitinib dose reductions (n=4). All four baricitinib dose reductions greater than 25% in group B resulted in a disease flare and fulfilled the flare criteria within 60** days. The proportion of flares in group A (20%) versus group B (100%) was significantly different (p=0.012). The time to flare in both groups was evaluated by Cox proportional hazards models and displayed using Kaplan-Meier curves. *P1 developed clinical symptoms with one laboratory abnormality postdose reduction and although he had a clinical flare, he did not fulfil the flare criteria and is not included in the count. **P7 developed symptoms several days after baricitinib dose reduction however did not have a blood draw until 55 days later when the disease was still active. P7 fulfilled the flare criteria on day 55 postdose reduction when the laboratory markers were available.

was 254.46 (IQR 267.56) in the low-dose period, significantly higher compared with the high-dose period 45.93 (IQR 117.78) (p <0.0001) (online supplemental figure 4). Ranges of cut-off values of clinical and subclinical flare visits identified during the high-dose and low-dose visits and clinical scenarios that illustrate the use of the flare criteria are listed in the (online supplemental tables 6b and 7).

Addition of IFN score criterion to the CANDLE/PRAAS disease flare criteria

The IFN score was assessed before and after dose reduction in 8 of 14 instances of dose reductions. It increased by >500% in P1 who had a clinical flare and remained within normal values in P4 who had a subclinical flare (online supplemental figure 1). Among six patients who did not fulfil flare criteria (seven visits), the IFN score increased by 233% in one patient (P1) (one visit), did not change or remained within normal limits in five patients (five visits). IFN score was not available in one visit (P4 second visit) (online supplemental table 6a).

In a subanalysis, we included the IFN score as biomarker criterion and determined the same cut-off of ≥20% that we used for ESR. Addition of the IFN score criterion to the proposed flare criteria increased the proportion of visits that patients fulfilled flare criteria (clinical and subclinical) from 37.93% to 58.62%, during the low-dose period and from 10.13% to 20.25% during the high-dose period; the difference remained significant (p<0.001) (online supplemental figure 5).

DISCUSSION

In this retrospective study, we observed substantial rebound inflammation and disease flares with baricitinib dose reduction. These findings allowed to develop flare criteria to assist with monitoring of disease activity, and to be used in designing clinical trials in CANDLE/PRAAS.

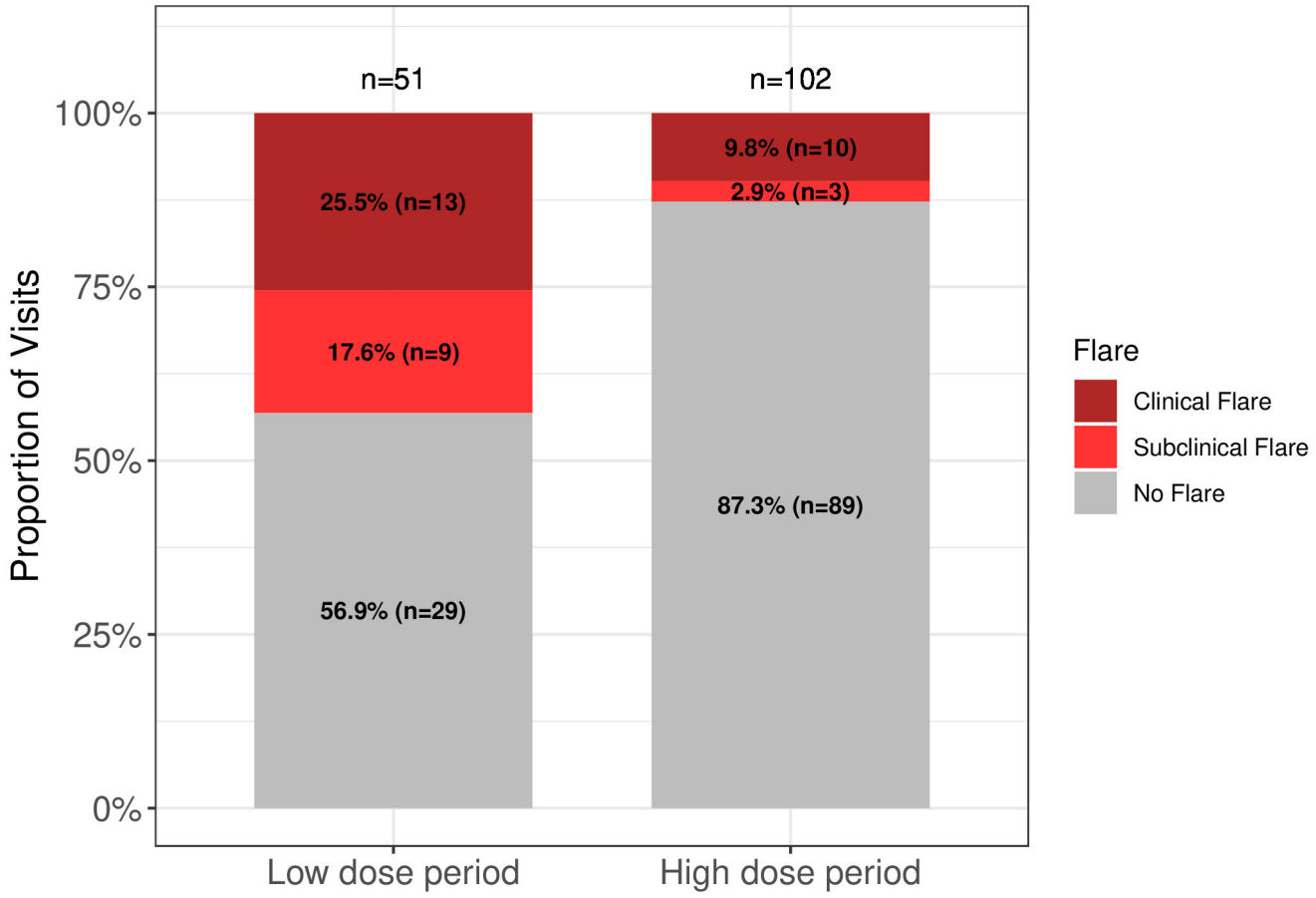

Figure 4 Proportion of disease flares comparing low-dose baricitinib visits to high-dose baricitinib visits. A total of 153 visits in 6 patients who had both high-dose (n=102) and low-dose (n=51) visits were identified and assessed. The proportion of visits that patients fulfil flare criteria during the low-dose period (43.14%) is significantly higher (p<0.0001) than during the high-dose period (12.75%). The proportion of visits that patients fulfil flare criteria during the low-dose and high-dose period was compared by using a two-sided χ^2 test of homogeneity.

We observed more disease flares in patients with a larger dose reduction. In one patient, abrupt drug discontinuation triggered the development of MAS. Rebound flares with drug reductions and discontinuations are commonly seen in autoinflammatory diseases.[8–10] Rebound flares are of particular concern when drugs with short half-lives are withdrawn, as they can trigger sudden, severe flares that can lead to organ damage. Serious withdrawal symptoms are well documented in patients withdrawing psychopharmaceutics that have short half-lives, including antidepressants and narcotics,[11 12] but this is not generally considered in patients with systemic inflammation. In patients with interferonopathies, baricitinib dose adjustments may be necessary to reduce exposure and to limit baricitinib-related side effects, such as cytopenias and to reduce BK viral load in the blood to keep with safety standards developed for renal transplant recipients.[13–15] In patients who achieve disease control on baricitinib, the lowest effective dose to maintain disease control should be sought.

Due to differences in pharmacokinetics in children and adults,[3] which is caused by increased drug clearance and a higher volume of distribution in children, higher drug doses and shorter dosing intervals may be required in children to achieve similar exposure to adults. Dose decreases are therefore necessary as children grow and gain weight. Our data indicate that dose reductions should be implemented slowly and gradually and need to be carefully monitored.

Defining and validating disease outcomes and/or activity criteria in patients with ultrarare diseases remains an ongoing challenge.[16] Validated outcomes in autoinflammatory diseases have so far only been defined for IL-1 mediated diseases and focus on the definition of disease remission[17 18] or the reduction of a disease symptom score coupled with CRP.[9] Instruments to assess disease symptoms include a DDS and/or a disease activity questionnaire such as the autoinflammatory diseases activity index (ADAI) that is assessed during disease attacks.[19 20] Overall, these disease activity outcomes and flare descriptions align with accepted endpoints suggested for patients with juvenile idiopathic arthritis.[21] We had defined remission for CANDLE/PRAAS,[1] but disease flare criteria have not been developed. Our systematic analysis of patients' flares by assessing paired visits before and after baricitinib dose reductions allowed extraction of parameters that changed during disease flares including concomitant increases in acute phase reactants, a drop in WBC, ALC and in PLT count. The degree of change in HGB was much smaller compared with the change observed in the other markers. We however kept HGB as a flare criterion, as we measured only acute changes, as in longer duration of suboptimal care, more pronounced HGB changes are usually seen.

A chronically elevated peripheral blood IFN signature is a hallmark of incompletely treated CANDLE/PRAAS. Prolonged normalisation of the IFN signature has so far only been seen in a subset of patients with CANDLE/PRAAS who carry autosomal recessive *PSMB8* mutations treated with JAKis including baricitinib.[1] Our study suggests that addition of the IFN score criterion captures more disease flares that were associated with DDS increases and thus associated with clinical symptoms and

increased the sensitivity of detecting a flare in particularly in lymphopenic patients who had low CRP. Inclusion of the IFN score as laboratory criterion identified six clinical flares that were not identified using the clinical flare criteria without the IFN score. Caveats when using the IFN score include substantial fluctuation in a given day[3] when patients are not in remission. In active patients, a 20% variation in a single day does not flag a disease flare and variations should be interpreted with caution. The IFN score inclusion as criterion for disease flare is therefore only useful in patients with well-controlled disease who can normalise the IFN score. The proposed flare criteria without IFN score can be used in settings where the IFN score assessment is not routinely available. In clinical studies, inclusion of the IFN score to the proposed flare criteria would increase the number of flare visits detected particularly in patients with chronic cytopenias.

In this study, we assessed the disease criteria during periods when patients were treated with high-dose baricitinib, reflecting treatment with currently recommended doses,[3] and during low-dose visits when patients received doses below those that are currently recommended. The criteria identified disease flares during these periods by comparing them to a reference visit that was established when patients were well controlled. Although the need for a reference can be considered a 'limitation', in practical terms it makes little sense to determine disease flares in patients with CANDLE/PRAAS who have chronically active disease. Comparing disease activity to periods when the disease is controlled allows an individualised assessment of flares and treatment adjustments and assists in longitudinal monitoring of disease activity. The criteria do not currently adjust for high glucocorticoid doses. However, when reference visits were established in our study, all patients were either off glucocorticoids and fulfilled remission criteria[1] (P4, P5 and P10) or had more than 50% reduction (mg/kg/day) from baseline (P1, P3, P6 with P3 fulfilling remission criteria on low doses of glucocorticoids), except P7 whose glucocorticoid dose was maintained at a high dose to prevent disease flares in the context of baricitinib reduction and withdrawal due to the development of BK nephropathy.

The proposed flare criteria can serve as a valuable tool, empowering healthcare professionals to systematically monitor disease activity. The flare criteria may be particularly useful in assessing patients when lowering glucocorticoid or baricitinib dose and when evaluating the necessity for intensifying JAKi therapy in patients who develop postdose reduction flares. The criteria can also be used to make baricitinib dose adjustments during growth. The proposed flare criteria may become useful but require validation in other interferonopathies including Aicardi-Goutières syndrome (AGS) and stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) when treatments become available that achieve similar disease control to JAKis in CANDLE/PRAAS. In addition to the value of these criteria in monitoring and objectively quantifying disease flares over time, the criteria can also be used to assess disease flares in clinical trials that randomise patients who achieved disease control to continued investigational drug use or placebo or standard of care control.[22] Our flare criteria and assessment of flare rates during high-dose and low-dose visits facilitate powering clinical trials in patients with CANDLE/PRAAS but also caution that abrupt withdrawals can result in severe rebound such as MAS.

There are limitations to this study. The study was conducted retrospectively and did not have a prespecified control arm; the sample size is small. Further validation of the proposed flare criteria is warranted through testing in larger series and clinical trials. A strength is the prospective evaluation of patients for a median of 6.9 years which allowed the inclusion of 153 patient visits with complete laboratory evaluations. The criteria generated can also be used to generate data on disease flare rates in natural history studies in rare inflammatory diseases that can serve as comparison in the assessment of treatment interventions in rare diseases. Comparing treatment data to historical control data have been proposed as acceptable for regulatory approval of treatments for ultrarare diseases.[23]

In conclusion, our data should raise awareness of rebound inflammation during baricitinib dose reduction and alert caretakers to establish monitoring procedures in patients requiring dose adjustments. The 'proposed disease flare criteria' can aid in monitoring treatment response by assessing flare rates and in designing clinical trials in CANDLE/PRAAS in the future.

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I. Supplementary Methods

1. PATIENTS AND INCLUSION AND EXCLUSION CRITERIA

All patients were co-enrolled in the NIH Natural History Protocol of Autoinflammatory Diseases (NCT02974595).

a. **Initial assessment**
Ten patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/ proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS) treated with baricitinib were included in this retrospective review. Nine out of 10 patients had baricitinib dose reductions and one patient (P8) did not have a dose reduction during the study period (supplementary table 1). Seven patients (P1, P3, P4, P5, P6, P7, P10) had baricitinib dose reduction below the clinically effective dose and two patients (P2 and P9) had minimal dose reduction. Patients with baricitinib dose reductions were included to assess clinical and laboratory symptoms during pre- and post-baricitinib dose reduction periods.

b. **Development of CANDLE/PRAAS Clinical and Subclinical Disease Flare Criteria**
Post baricitinib dose reduction, five patients (P1, P3, P5, P6, P10) developed clinical symptoms (in addition to laboratory changes) consistent with CANDLE/PRAAS disease flares and two patients (P4 and P7) developed laboratory changes alone that were consistent with disease flare. Data were used from these seven patients to develop CANDLE/PRAAS disease flare criteria.

c. **Assessment of the CANDLE/PRAAS Disease Flare Criteria in visits stratified into high dose and low dose visits**
Six patients (P1, P3, P4, P5, P6, P10) had several visits on low and high baricitinib doses and were included in assessment of the CANDLE/PRAAS flare criteria during visits on high doses and low doses of baricitinib. Patients 2 and 9 were excluded as they did not have a low dose period. Patient 8 was excluded since patient did not have a dose reduction during the study period. Patient 7 was excluded (he was included to development of flare criteria) since patient developed azotemia secondary to presumed BK nephropathy and baricitinib was subsequently discontinued.[1]

2. DAILY DIARY SCORE (DDS) ASSESSMENT

Disease-specific patient daily diary for CANDLE/PRAAS were collected prospectively during JAGA program.[1] Patients with CANDLE/PRAAS or their parents recorded daily symptoms of fever, rash, musculoskeletal pain, headaches, and fatigue. Each symptom was rated on a scale of 0 to 4, with 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=more severe symptoms, and 4=severe symptoms (possible range 0- 20). At each visit, the diary score was calculated as follows:

a. Average score of each symptom was calculated using data entered since the previous visit and correcting for any day for which diary scores were not recorded.
b. The calculated average score for each symptom was summed up and divided by the number of assessed symptoms to calculate the average score for each patient.

Retrospectively reviewed and analyzed DDS data for assessment of baricitinib dose reduction associated clinical flares. Mean DDS was calculated for the period of seven days including the period of three days before dose reduction, day of dose reduction and three days after dose reduction.

If the mean DDS of the reference visit was zero and a patient developed any symptoms during a subsequent visit, it was considered to be a significant change. Therefore, a mean DDS greater than zero is considered indicative of a clinical flare for these patients**.**

The percent (%) changes in DDS and the laboratory biomarkers were compared between the last visit before dose reduction and the first visit after dose reduction (supplementary table 6a).

3. DATA EXTRACTION

a. Development of CANDLE/PRAAS Clinical and Subclinical Disease Flare Criteria

For all visits with dose reductions, clinical and laboratory data were extracted from the last visit prior to baricitinib dose reduction (reference visit), and the first follow-up visit after the dose was reduced (flare visit). Data included DDS, C-reactive protein (CRP), erythrocyte

sedimentation rate (ESR), white blood cell count (WBC), hemoglobin (HGB), absolute lymphocyte count (ALC), platelets (PLT), and 25-gene IFN score[2] (when available). Physician notes were reviewed for documentation of clinical symptoms and physical exam findings. Absolute and percent changes were calculated (supplementary table 6a).

b. Assessment of the CANDLE/PRAAS Disease Flare Criteria in visits stratified into high dose and low dose visits

The visit prior to dose reduction was used as a reference visit to calculate post dose reduction changes. For the assessment of the established disease criteria in high-dose and low-dose visits, we determined a reference visit for each patient separately when the patient was on optimal/clinically effective baricitinib dose and clinically stable considering his/her own disease course, based on expert rheumatologist judgement. For the reference visit, all patients were clinically stable or fulfilled remission criteria that was published by Sanchez et al.[1] Three patients (P4, P5 and P10) were in remission and off glucocorticoid (GC)s. Three patients (P1, P3 and P6) had more than 50% reduction in their daily GC dose from baseline. Patient 7 had reduction in his GC dose from baseline (1.2 mg/kg/day at first JAGA visit) however he was still on 0.82 mg/kg/day GCs at reference visit since he had azotemia and his baricitinib dose was reduced. Laboratory changes after dose reductions that resulted in a clinical flare and laboratory changes after dose reductions that did not result in a clinical flare were systematically evaluated.

For the criteria, DDS increases were used to define clinical symptoms. In a sub-analysis, we assessed the value of adding the IFN score as a laboratory biomarker to increase the sensitivity of disease flare detection and computed the number of additional clinical and subclinical flares that were identified.

4. DEVELOPMENT OF CANDLE/PRAAS DISEASE FLARE CRITERIA

Definition and clarification of data extraction: The number of baricitinib dose reductions, reasons for the dose reductions, the amount of dose reduction, and the first date when the patient took the lower dose were documented. Data were extracted in an excel spreadsheet.

Assessment of daily diary score changes: Clinical notes and daily diaries were retrospectively reviewed for the periods baricitinib dose reductions occurred. Laboratory biomarkers of inflammation and clinical symptoms recorded on a daily diary and/or clinical notes that can constitute a disease flare including fever, rashes, headaches, fatigue, and joint and musculoskeletal pain were extracted. In some instances image of rashes were sent by e-mail. Clinically relevant changes in laboratory biomarkers were included as flare criteria and confirmed previous clinical observations reported in patients with interferonopathies during active disease.[3 4]

Definition of abnormal biomarker cut off values: CRP was considered a clinically abnormal value if 5mg/L or greater, and ESR was considered a clinically abnormal value if 20 mm/hr or

greater. CRP either remained within normal limits or increased to above 5mg/L. Increasing CRP values were a component of the flare criteria. When CRP increased to higher than 5mg/L, the % change was computed. In addition to the change in CRP score resulting in a clinically abnormal value, a cutoff of a 40% increase in CRP was considered a change in cases when the CRP was elevated in the reference visit and a cutoff of a 20% increase in ESR was considered a change in cases when the ESR was elevated in the reference visit. We used the same cut off of 20% and requirement of the change resulting in a clinically abnormal value for IFN score.

Determination of % change in biomarker cut off values: We assessed the laboratory changes at the reference visits and the visits when the patients developed a disease flare post dose reduction (supplementary table 6a) We calculated the % change (increase or decrease) in each laboratory biomarker for each patient comparing the reference visit with the flare visit. Then we determined the lowest meaningful % change for each laboratory biomarker that was associated with clinical symptoms and was consistent with a clinically meaningful change in biomarker. We used these percentages as cut off when developing the flare criteria. We subsequently applied these criteria to all visits to identify possible flare visits during both the low dose and the high dose periods and assessed the % changes to those visits identified as flare visits by using the criteria. The % changes were similar in the high dose and low dose flare visits in the confirmation phase (supplementary table 6b) to those in the baricitinib withdrawal flare visits, which strengthened the notion that the cut off values selected were meaningful in long-term monitoring settings.

5. CONFIRMATION OF THE CANDLE/PRAAS DISEASE FLARE CRITERIA

Definition of a visit: Patients had study visits with clinical and laboratory evaluations, every 3-6 months on average at NIH. However, they were also seen by their local providers and had disease monitoring labs performed in between NIH visits. A patient in a disease flare who requires close monitoring by their local provider may require more frequent clinical and laboratory evaluations. To prevent overinterpretation of data obtained from a period where patients were in states of prolonged disease flare, we determined that each calendar month represents a visit if the patient had clinical and/or laboratory evaluation. If a patient had blood work at multiple occasions within the same calendar month, those multiple visits were considered as one study visit and labeled as flare vs no flare visit based on the worst clinical and laboratory findings. e.g., if a patient had blood work 3 times in a given calendar month and 1 out 3 was consistent with disease flare, we considered this visit as a flare visit.

Definition of high-dose and low-dose visits: To assess the performance of the flare criteria, we assessed the flare criteria during visits when patients received currently recommended dose/clinically effective dose (supplementary table 4),[15] and lower than effective dose. Patient visits on lower doses were categorized as “low-dose” visits and those on equal or higher than effective/recommended doses were categorized as “high-dose” visits. In this analysis we only included patients who had both, “low dose” and “high dose” visits (n=6; P1, P3, P4, P5, P6 and P10). We excluded a total of four patients: three patients who had no “low dose” visits (P2, P8 ad P9) and one patient who had azotemia (P7). Patient 7 was excluded since determining the

clinically effective baricitinib dose in the setting of azotemia and renal insufficiency may not be accurate.

We identified 51/153 visits when patients received low dose baricitinib and 102/153 visits when patients received high dose baricitinib, over 9.5 and 25.2 patient years respectively. The same reference visit for each patient was used for comparison with each visit in the low dose and each visit in the high dose period. The clinical and subclinical CANDLE/PRAAS flare criteria were used to calculate the flare rate during low-dose and high-dose visits.

Treatment decisions (steroid adjustments/baricitinib adjustments/no action) during "flare visits": To determine whether clinical and subclinical "flare visits" that were identified by systematic application of the flare criteria had treatment actions implemented in at the time of the visit, we extracted the drug changes and the impact on disease activity on subsequent visits.

BK viral load extraction before and after dose reduction: To assess the impact of the baricitinib dose reduction on viral load in blood and urine, we extracted the viral load at the visit before and after dose reduction and compared whether the load was lower, the same or higher.

IFN score addition as biomarker in a sub analysis:
The 25-gene IFN score[2] was collected as a secondary endpoint in the compassionate use study[1] but was initiated later and was therefore not available for all study visits. Based on control data, a normal IFN score was defined as below 44.2 (cut off is 95%ile in healthy controls).[2]

In the baricitinib reduction visits, the 25-gene IFN score was only available before and after dose reduction for one patient (P1) out of the seven patients who developed a clinical flare post baricitinib dose reduction. The IFN score rose highly when the baricitinib dose was reduced in patient (P1). The original flare criteria were therefore established without the inclusion of the IFN score due to paucity of data. However, for the validation comparing high-dose and low-dose visits, the 25-gene IFN score was available for 108 out of 153 visits, which allowed us to assess the performance of the IFN score at high-dose and at low-dose visits. The median [IQR] IFN score was 45.93 [117.78] in high dose period and 254.46 [267.56] in low dose periods in patients. Difference between median IFN score in low dose versus high dose period was significant ($p<0.0001$) by using two-sided Wilcoxon Rank Sum test.

We then assessed the flare criteria by adding the IFN score to determine whether the flare criteria could capture more "flare visits". The addition of the IFN score to the flare criteria was assessed by determining how many additional flares were identified.

II. Supplementary Tables

Supplementary Table 1 Baricitinib dose reductions and effects on BK viremia/viruria

Patient	# Dose Reduction	Study day Pre- and post-reduction baricitinib dose	Dose Reduction by mg (%)	Reason for Dose Reduction	Effect of the baricitinib dose reduction on BK viremia/viruria
P1	#D1*	1342 from 9 mg/day to 7 mg/day	2 (22)	Intentional: Identify minimal dose that suppresses disease in the context of BK viruria (7.13 log_{10} copy/mL) **BK viremia (low positive <3.7 log_{10} copy/mL)**	BK viruria decreased to 6.6 log_{10} copy/mL ***BK viremia resolved***
P2	#D2	1234 from 7 mg/day to 6 mg/day	1 (14)	Intentional: Identify minimal dose that suppresses disease in the context of BK viruria (3.67 log_{10} copy/mL) No BK viremia	BK viruria decreased to 3.33 log_{10} copy/mL No BK viremia
P3	#D3*	720 from 10 mg/day to 6 mg/day	4 (40)	Intentional: Anemia (presumed to be baricitinib triggered) BK viruria NA **BK viremia <250 copies/ml**	BK viruria NA ***BK viremia resolved*** Anemia resolved
	#D4*	1080 from 8 mg/day to 6 mg/day	2 (25)	Intentional: Identify minimal dose that suppresses disease in the context of BK viruria (>8.7 log_{10} copy/mL) **BK viremia (4.84 log_{10} copy/mL)**	BK viruria decreased to 7.98 log_{10} copy/mL ***BK viremia decreased to 3.8 log_{10} copy/mL***
	#D5	2717 from 8 mg/day to 7 mg/day	1 (12)	Intentional: Identify minimal dose that suppresses disease in the context of BK viruria (>8.6 log_{10} copy/mL) **BK viremia (4.1 log_{10} copy/mL)**	No data on BK viruria data ***BK viremia decreased to 3.7 log_{10} copy/mL***
P4	#D6	981 from 10 mg/day to 4 mg/day	6 (60)	Accidental: Patient ran out of medication and reduced dose to stretch baricitinib until his NIH visit	Not applicable as patient was on the lower dose for only 3 days
	#D7	1061 from 10 mg/day to 9 mg/day	1 (10)	Intentional: Identify minimal dose maintaining remission in the context of BK viruria (3.56 log_{10} copy/mL) No BK viremia	BK viruria (low viral load prior to dose reduction) remained largely unchanged at relatively low copy numbers, 3.76 log_{10} copy/mL No BK viremia
	#D8	1903 from 9 mg/day to 8mg/day	1 (11)	Intentional: Increased viral warts BK viruria (5.8 log_{10} copy/mL) No BK viremia	BK viruria decreased to 3.8 log_{10} copy/mL No BK viremia
P5	#D9*	1110 from 11 mg/day to 9 mg/day	2 (18)	Intentional: Identify minimal dose maintaining remission in the context of BK viruria (4.98 log_{10} copy/mL) No BK viremia	BK viruria decreased to 4.12 log_{10} copy/mL No BK viremia
P6	#D10	839 from 6 mg/day to 4 mg/day	2 (33)	Intentional: Identify minimal dose that suppresses disease in the context of BK viruria (5.8 log_{10} copy/mL) No BK viremia	BK viruria decreased to 4.36 log_{10} copy/mL No BK viremia
P7**	#D11a&	812 held off for one day	5.4 (100)	Intentional: BK viremia 6.37 log_{10} copy/mL (BK viruria 10.16 log_{10} copy/mL)	see below&

		(from 5.4 mg/day)			
	#D11b[&]	820 Discontinuation of baricitinib (from 0.9 mg/day)	0.9 (100)	Intentional: Renal failure/Azotemia (presumed BK nephropathy)	Patient continued to have BK viruria $\geq$ 8.9 log_{10} copy/mL and BK viremia $\geq$ 5.99 log_{10} copy/mL in the context of renal failure
P8		No dose reduction during the study period		Not applicable	Not applicable
P9	#D12	216 from 10 mg/day to 8 mg/day	2 (20)	Intentional: Increase in frequency of headaches	No data on BK viruria and viremia pre-dose reduction
P10[#]	#D13	521 from 12 mg/day to 10 mg/day	2 (17)	Intentional: Identify minimal dose maintaining remission in the context of BK viruria (9.75 log_{10} copy/mL) No BK viremia	No data on BK viruria (on lower dose of baricitinib) No BK viremia
	#D14	899 from 12 mg/day to 11 mg/day	1 (8)	Intentional: Identify minimal dose maintaining remission in the context of BK viruria (10.28 log_{10} copy/mL) **BK viremia (4.15 log_{10} copy/mL)**[^]	BK viruria >8.6 log_{10} copy/mL ***BK viremia decreased to 3.1 log_{10} copy/mL****

D, dose; NA, not available; P, patient

[*]P1: Baricitinib dose was reduced from 9 mg/day to 8 mg/day and then to 7 mg/day four days later, P3: Baricitinib dose was reduced from 10 mg/day to 8 mg/day and then to 6 mg/day the following day. P3: Baricitinib dose was reduced from 8 mg/day to 7 mg/day and then to 6 mg/day 11 days later. P5: Baricitinib dose was reduced from 11 mg/day to 10 mg/day and then to 9 mg about four weeks later.

[**]Patient 7 had one additional dose reduction from 8 mg/day to 6mg/day by patient's local provider at another time point, due to anemia during a hospitalization for a presumed CANDLE/PRAAS disease flare. Baricitinib dose was increased to 8 mg/day 3 weeks later and no laboratory data is available for this dose reduction. This dose reduction was excluded since a. the patient had been admitted with a presumed CANDLE/PRAAS disease flare prior to baricitinib dose reduction, b. missing data for this time frame.

[&]Patient 7's dose reduction started with dose reduction from 8 mg/day to 6 mg/day. Then rapid dose reduction and discontinuation occurred over 3 months in the context of renal failure. Flare occurred with holding baricitinib for one day although it was restarted at a dose of 2.7 mg/day the following day. It was discontinued permanently one week later. After discontinuation of baricitinib, he continued to have active disease that was controlled with high doses of glucocorticoids. He had a major flare presenting as macrophage activation syndrome (MAS). One week after discontinuation of baricitinib, the patient was admitted for persistent fevers, tachycardia, abdominal distention and fluctuating increased work of breathing with increased oxygen requirement.

[#]D13 occurred on study day 521. P10's baricitinib dose was increased from 10 mg/day back to 12 mg/day eventually. On study day 899, P10 had another dose reduction (D14) from 12 mg/day to 11 mg/day.

[^]In addition, patient 10 had mistakenly taken extra dosing (24 mg/day instead of 12 mg/day) for 45 days since he mixed up 4mg vs 1 mg tablets

Baricitinib dose reductions by 1-2 mg/day resulted in lower BK viral load in the blood and urine. BK viremia became negative in P1 and decreased in P3 and P10. With the development of BK nephropathy in one patient (P7), we recommend monitoring BK viremia and suggest keeping BK viral load in blood as low as possible, but all times below log 4 copy/ml (10,000 copies/ml), consistent with recommendations made for kidney transplant recipients.[6 7]

Supplementary Table 2 Summary of post-baricitinib dose reduction clinical symptoms and outcomes of clinical flare vs no clinical flare

Patient/Dose reduction (% Dose change)*		Mean DDS (0-4)	Post Dose Reduction Worsening Clinical Symptoms (Yes/No)	Clinical Flare based on Clinical Judgement (Yes/No)
P1/D#1 (22%)	Pre-dose reduction visit	0.3714	Yes (headaches, oral ulcers, MSK pain, fatigue)	Yes
	Flare Visit	0.428		
	% Change	**15**		
P2/D#2 (14%)	Pre-dose reduction visit	0	No	No
	First visit post dose reduction	NA		
	% Change	NA		
P3/D#3 (40%)	Pre-dose reduction visit	0.13	Yes (fever and rash)	Yes
	Flare Visit	0.4		
	% Change	**208**		
P3/D#4 (25%)	Pre-dose reduction visit	0	Yes (intermittent rash, fever, MSK pain)	No**
	First visit post dose reduction	0.3		
	% Change	**>100**		
P3/D#5 (12%)	Pre-dose reduction visit	0	Yes (intermittent mild rash and MSK symptoms)	No**
	First visit post dose reduction	0.11		
	% Change	**>100**		
P4/D#6 (60%)	Pre-dose reduction visit	0	No	No^
	Flare Visit	0		
	% Change	0		
P4/D#7 (10%)	Pre-dose reduction visit	0.54	No	No
	First visit post dose reduction	0		
	% Change	- >100		
P4/D#8 (11%)	Pre-dose reduction visit	0	No	No
	First visit post dose reduction	0		
	% Change	0		
P5/D#9 (18%)	Pre-dose reduction visit	0.028	Yes (severe headaches and fever)	Yes
	Flare Visit	0.142		
	% Change	**407**		
P6/D#10 (33%)	Pre-dose reduction visit	0.2	Yes (intermittent fevers, fatigue, and rash)	Yes
	Flare Visit	0.31		
	% Change	**55**		
P7/D#11 (100%)	Pre-dose reduction visit	NA	No	No^
	Flare Visit	NA		
	% Change	NA&		
P9/D#12 (20%)	Pre-dose reduction visit	0.114	Yes (fatigue only)	No**
	First visit post dose reduction	0.2		
	% Change	**75**		
P10/D#13 (17%)	Pre-dose reduction visit	0	Yes (periorbital edema with erythema, facial panniculitis, and localized inflammation around thumb)	Yes
	Flare Visit	0.314		
	% Change	**>500**		
P10/D#14 (8%)	Pre-dose reduction visit	0.057	No	No
	First visit post dose reduction	0.028		
	% Change	-50		

Pre-dose reduction visit (=reference visit): Last visit occurred prior to dose reduction.
Flare visit: First visit occurred after baricitinib dose reduction.
*see supplementary table 1 for dose reductions

** Three dose reductions (P3/D#4, P3/D#5, P9/D#12) resulted in changes in DDS and they had labs drawn 2 weeks, 3 months, and 2.5 weeks after recording of the symptoms in DDS respectively. At that time there were no laboratory changes observed. We did not consider these DDS as disease flares.
P3: We observed mild and intermittent rash and MSK symptoms at pre dose reduction visits as well; these symptoms were considered baseline fluctuations. P9: Patient developed fatigue only and DDS change was secondary to fatigue. In the absence of additional CANDLE/PRAAS findings such as fevers, rashes, MSK symptoms, headaches, it was considered to be insufficient to call this as a disease flare. Patient was asymptomatic otherwise.
^P4 received lower dose of baricitinib for three days. Patient had clinically significant laboratory changes post dose reduction with no clinical symptoms. P7's baricitinib was discontinued secondary to azotemia and was on high dose steroids. P7 had clinically significant laboratory changes post dose reduction with no clinical symptoms (both patients fulfilled subclinical flare criteria, please see supplementary table 6a).
D, dose reduction; DDS, daily diary score; NA, not available; P, patient.

Supplementary Table 3 Summary of laboratory biomarkers, mean DDS, glucocorticoid data and clinical status at reference visits for patients included in the confirmation of the flare criteria

Patient*	Mean DDS**	CRP (mg/L)	ESR (mm/hr)	WBC (k/uL)	HGB (g/dL)	PLT (k/uL)	ALC (k/uL)	GC dose (mg/kg/day)	Clinical status
P1	0.37142857	0.20	2.00	5.40	14.10	356	1.12	0.3	Stable disease (S)
P3	0.13	0.7	40	6.43	7.1^	194	1.52	0.14	Minimal disease activity (MDA)
P4	0	3.5	5	7.47	16.6	230	2.47	Off GCs	Remission (REM)
P5	0.028	3.3	8	6.42	15	200	3.02	Off GCs	Remission (REM)
P6	0.2	0.40	18.00	9.98	12.40	394	0.90	0.33	Stable disease (S)
P10	0	1.2	4	4.23	14.2	341	1.2	Off GCs	Remission (REM)

*P7 was not included in the confirmation phase as he was considered to have active disease and remained on high doses of GC.
**Retrospectively reviewed and analyzed DDS data for assessment of baricitinib dose reduction associated clinical flares. Mean DDS was calculated for the period of seven days including the period of three days before dose reduction, day of dose reduction and three days after dose reduction. If the mean DDS of the reference visit was zero and a patient developed any symptoms during a subsequent visit, it was considered to be a significant change. Therefore, a mean DDS greater than zero is considered indicative of a clinical flare for these patients.
^Low hemoglobin was drug related (baricitinib induced anemia)
ALC, absolute lymphocyte count; CRP, C-reactive protein; DDS, daily diary score; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HGB, hemoglobin; IFN, interferon; P, patient; PLT, platelets; WBC, white blood cell.

At the time of dose reduction, patients P1 and P6 had stable disease (S), P3 had minimal disease activity (MDA), and patients P4, P5, P6 were in clinical remission (REM). See previous definition of remission: DDS<0.15, CRP<5mg/L, off GC. (Sanchez G et al. JCI 2018). We have defined minimal disease activity as: DDS<0.15, CRP<5mg/L and GC less than 0.15mg/kg/day (prednisone equivalent) and stable disease as stable DDS, CRP<5mg/L and stable dose of GC of <0.35mg/kg/day (prednisone equivalent).

Supplementary Table 4 Summary of baricitinib dosing regimen at the time of baricitinib dose reductions

Patient ID	Age at enrollment (years)	Study day reached minimally required optimal dosing	Minimally required optimal dosing (mg/day)[*1]	Study day of dose escalation	Clinically effective baricitinib dose (mg/day)	Study day of baricitinib dose reduction	Baricitinib dose at time of dose reduction (mg/day)
P1	7.3	407	6	820	8	977	7
P3	6.2	127	6	566	8	721	6
P4	19.3	178	8	353	8[**]	982	4
P5	15.8	157	9	164	10	1110	9
P6	2.3	281	4	635	6	839	4
P7	3.5	268	4	396	8	812	0[***]
P10	19.7	148	9	225	11	521	10

[*]Based on Sanchez et al. J Clin Invest. 2018 Jul 2;128(7):3041-3052.
[**]P4 had a dose escalation to 10 mg/day on study day 353 with an attempt to identify the clinically effective dose but later remained stable on 8 mg/day which was determined as clinically effective dose for P4.
[***]P7's dose reduction started with dose decrease from 8 mg/day to 6 mg/day. Then rapid dose reduction and discontinuation occurred over 3 months in the context of renal failure. Flare occurred with holding baricitinib for one day although it was restarted at a dose of 2.7 mg/day the next day. It was discontinued permanently one week later.

Supplementary Table 5 Baseline demographics and clinical characteristics

	Value (%)		**Value (%)**
Age at enrollment— yr. mean (min-max)	11.5 (2.3-19.7)	**DMARDS prior to baseline §– no.**	10 (100)
Age group — no. (%)		≥2 DMARDS prior to baseline	7 (70)
0-2 yr	1 (10)	Mean number of DMARDS used prior to baseline (min-max)	3.2 (1-6)
3–6 yr	2 (20)	**Biologics prior to baseline §§– no. (%)**	8 (80)
7–10 yr	2 (20)	≥2 Biologics prior to baseline	7 (70)
11–18 yr	2 (20)	Mean number of biologics used prior to baseline (min-max)	2.8 (0-6)
≥18 yr	3 (30)	**Chronic oral glucocorticoid use §§§ - no. (%)**	8 (80)
Sex – no. (%)		Mean exposure to oral glucocorticoids – yr (min-max)	6.7 (1.5-16)
Male	7 (70)	**Clinical manifestations – no. (%)**	
Race or ethnic group – no. (%)		Panniculitis-induced lipodystrophy	10 (100)
White	5 (50)	Joint contractures	10 (100)
Black	2 (20)	Myositis‡	8 (80)
Hispanic	3 (30)	Metabolic syndrome*	6 (60)
By Genetic Diagnosis – no. (%)†		Systemic inflammation¶	10 (100)
PSMB8	6 (60)	Pulmonary arterial hypertension	1 (10)
PSMB4	1 (10)	Basal ganglia calcifications	7 (70)
PSMB4/PSMB9	2 (20)	Anemia	9 (90)
PSMB8/PSMA3	1 (10)	Lymphopenia	5 (50)
Autoantibodies		Height < 3rd percentile	8 (80)
ANA	2(20)	Weight < 3rd percentile	6 (60)
RF	1(10)		
Anti-CCP	0 (0)		

†*PSMB8* (n=5 homozygous, n=1 compound heterozygous), *PSMB4* (n=1 compound heterozygous), *PSMB4/PSMB9* (n=2 digenic), PSMA3/PSMB8 (n=1 digenic)

§ Azathioprine, Colchicine, Cyclosporine, Cyclophosphamide, Dapsone, Hydroxychloroquine, Methotrexate, Mycophenolate mofetil, Tacrolimus, Thalidomide

§§ Adalimumab, Abatacept, Anakinra, Canakinumab, Etanercept, Infliximab, IVIG, Tocilizumab

¶CRP, High Sensitivity >5.0 mg/L or Erythrocyte Sedimentation Rate (ESR) > 20 mm/hr. Patients 6 and 7 had systemic inflammation throughout their disease course however they did not have elevated CRP or ESR at baseline likely because they were on high dose glucocorticoids (> 1 mg/kg/day prednisone equivalent dose) at the time.

‡ Documented by bilateral thigh MRIs

*By Ford criteria, Ford et al. Diabetes care 2005; 28, 878-81

ANA, antinuclear antibody; anti-CCP, anti–cyclic citrullinated peptide, DMARDS, disease modifying antirheumatic drugs; RF, rheumatoid factor; yr, year.

Supplementary Table 6a Absolute values and percent changes of DDS and laboratory biomarker levels comparing the reference visit with the flare visit

Patient/ Dose reduction (% Dose change)*		DDS (0-4)	CRP (mg/L)	ESR (mm/hr)	WBC (k/uL)	PLT (k/uL)	ALC (k/uL)	HGB (k/uL)	IFN score (cut off 44.2)	Clinical flare (Judgement based)	Included to development of CANDLE/ PRAAS flare criteria	Fulfilling the CANDLE/PRAAS flare criteria/ Type of flare
P1/D#1 (22%)	Pre-dose reduction visit	0.3714	0.20	2.00	5.40	356.00	1.12	14.1	31.21	**Yes**	**Yes**	**No**
	Flare Visit	0.428	0.50	5.00	4.88	347.00	0.86	13.6	236.39			**Yes, when including IFN score criterion/ Clinical Flare^**
	% Change	**15**	WNL**	WNL**	-10	-2.5	**-23**	-4	**>500**			
P2/D#2 (14%)	Pre-dose reduction visit	0	4.2	55	5.34	215	1.84	12	11.36	No	No	No
	First visit post dose reduction	NA	0.9	23	5.61	206	2.27	11.9	3.36			
	% Change	NA	WNL**	-58	5	-4	23	-1	WNL**			
P3/D#3 (40%)	Pre-dose reduction visit	0.13	0.7	40	6.43	194	1.52	7.1	284.5^^	**Yes**	**Yes**	**Yes/Clinical Flare**
	Flare Visit	0.4	6.3	70	5.73	130	0.81	6.9	NA			
	% Change	**208**	**>500**	**75**	-11	**-33**	**-47**	-3	NA			
P3/D#4 (25%)	Pre-dose reduction visit	0	3.4	32	5.67	165	1.91	10.1	157.79	No	No	No
	First visit post dose reduction	0.3	1.9	32	5.19	133	2.04	9.2	187.8			
	% Change	**>100**	WNL**	0	-8	-19	-7	-9	19			
P3/D#5 (12%)	Pre-dose reduction visit	0	0.6	40	6.14	131	2.33	9.2	166	No	No	No
	First visit post dose reduction	0.11	<5	46	6	131	2	NA	NA			
	% Change	**>100**	WNL**	15	-2	0	-14	NA	NA			
P4/D#6 (60%)	Pre-dose reduction visit	0	3.5	5	7.47	230	2.47	16.6	40.19	**No**	**Yes**	**Yes/Subclinical Flare%**
	Flare Visit	0	36.9	8	4.7	225	2.09	15.8	35.20			
	% Change	0	**>500**	WNL**	**-37**	-2	**-15**	-5	WNL**			
P4/D#7 (10%)	Pre-dose reduction visit	0.54	0.7	2	5.74	257	2.26	15.5	8.17	No		No
	First visit post dose reduction	0	3.5	13	7.75	214	2.54	15.9	12.91			
	% Change	->100	WNL**	WNL**	35	-16	12	3	WNL**			
P4/D#8 (11%)	Pre-dose reduction visit	0	2.2	6	5.37	227	2.05	15.1	85.27	No	No	No
	First visit post dose reduction	0	5.5	13	5.6	246	2	15.1	45.93			
	% Change	0	**>100**	WNL**	4	8	-2	0	-46			
P5/D#9 (18%)	Pre-dose reduction visit	0.028	3.3	8	6.42	200	3.02	15	-6.96	**Yes**	**Yes**	**Yes/Clinical Flare**
	Flare Visit	0.142	6.3	NA	4.22	153	0.33	13.8	NA			
	% Change	**407**	**91**	NA	**-34**	**-24**	**-89**	-8	NA			
P6/D#10 (33%)	Pre-dose reduction visit	0.2	0.40	18.00	9.98	394.00	0.90	12.4	15.06	**Yes**	**Yes**	**Yes/Clinical Flare**

	Flare Visit	0.31	6.00	25.00	5.92	210.00	1.13	12.9	NA			
	% Change	**55**	**>500**	**39**	**-41**	**-47**	25	4	NA			
P7/D#11 (100%)	Pre-dose reduction visit	NA	0.30	58.00	10.12	135.00	1.47	10.3	-29.38	**No**	**Yes**	**Yes/Subclinical Flare**[%]
	Flare Visit	NA	0.90	NA	6.37	83.00	0.95	8.8	NA			
	% Change	NA	WNL**	NA	**-37**	**-39**	**-35**	-14	NA			
P9/D#12 (20%)	Pre-dose reduction visit	0.114	0.63	7	5.99	280	1.84	13.2	-15	No	No	No
	First visit post dose reduction	0.2	0.4	3	4.49	242	2.03	14.6	-17			
	% Change	**75**	WNL**	WNL**	**-25**	-13	10	10	WNL**			
P10/D#13 (17%)	Pre-dose reduction visit	0	1.2	4	4.23	341	1.2	14.2	102.99	**Yes**	**Yes**	**Yes/Clinical Flare**
	Flare Visit	0.314	27.95	62	2.73	296	0.53	12.6	NA			
	% Change	**>500**	**>500**	**>500**	**-35**	-13	**-56**	-11	NA			
P10/D#14 (8%)	Pre-dose reduction visit	0.057	<0.15	7	3.44	305	0.85	13.9	38.7	No	No	No
	First visit post dose reduction	0.028	0.6	5	4.11	332	0.95	13.8	129.4			
	% Change	-50	WNL**	WNL**	19	9	12	-1	**233**			

Pre-dose reduction visit: Last visit occurred prior to dose reduction. This visit for each patient who developed post dose reduction disease flares was used as a reference visit for evaluation of the flare criteria. Lowest value used to estimate a cutoff value is highlighted in blue. Values that are above the cut off are highlighted in orange.

Flare visit: First visit occurred after baricitinib dose reduction.

*see supplementary table 1 for dose reductions

**within normal limits before and during flare

^Patient fulfilled CANDLE/PRAAS disease flare criteria when including IFN score criterion to the flare criteria. Otherwise, patient was unable to meet required laboratory abnormalities to fulfill the flare criteria although patient developed clinical symptoms in association with baricitinib dose reduction.

^^IFN score not measured for this visit. Used the mean of IFN scores from the visits before and after the reference visit.

%Patient had clinically significant laboratory abnormalities post dose reduction, with no clinical symptoms. Therefore, patient fulfilled subclinical flare criteria.

ALC, absolute lymphocyte count; CANDLE/PRAAS, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; CRP, C-reactive protein; D, dose reduction; DDS, daily diary score; ESR, erythrocyte sedimentation rate; HGB, hemoglobin; IFN, interferon; NA, not available; P, patient; PLT, platelets; WBC, white blood cell; WNL, within normal limits.

Supplementary table 6b Ranges of cut-off values of clinical and subclinical flare visits identified during the high and low dose visit phases are in range with the changes seen in the acute baricitinib withdrawals.

Patient	Max and Min % Change	Mean DDS*	CRP % change (≥40% increase)	ESR % change (≥20% increase)	WBC % change (≥20% decrease)	HGB % change (≥15% decrease)	PLT % change (≥20% decrease)	ALC% change (≥15% decrease)
"Clinical Flare Visits"								
P1	Max % change	151	WNL	WNL	-34.8	-19.5	-3.5	-53.6
	Min % change	15.3	WNL	WNL	-20	-1.4	-0.5	-19.6
P3	Max % change	295	2571 (normal to abnormal)	75	-10.9	-2.82	-39.7	-46.7
	Min % change	23	900 (normal to abnormal)	15	-5.4	-2.82	-27.3	-46.7
P5	Max % change	1935.7	163.6 (normal to abnormal)	WNL	-40.8	-8	-29.5	-89
	Min % change	103.57	90.9 (normal to abnormal)	WNL	-11.8	-2	-11	-45.3
P6	Max % change	230	1400 (normal to abnormal)	38.9 (normal to abnormal)	-42.6	-15.3	-58.9	not applicable*
	Min % change	15	WNL	WNL	-29.9	-5.6	-33.5	not applicable*
P10	Max % change	Increased from zero, unable to calculate	2229 (normal to abnormal)	1450 (normal to abnormal)	-35.4	-15.5	-23.5	-69.2
	Min % change	Increased from zero, unable to calculate	665.8 (normal to abnormal)	900 (normal to abnormal)	-3.1	-9.9	-12.3	-24.2
"Subclinical Flare Visits"**								
P1	Max % change	not applicable	WNL	WNL	-32.78	-15.60	not applicable*	-22.32
	Min % change	not applicable	WNL	WNL	-32.78	-15.60	not applicable*	-22.32
P3	Max % change	not applicable	2100 (normal to abnormal)	192.5	-22.71	not applicable*	-41.75	-18.42
	Min % change	not applicable	1142.8 (normal to abnormal)	22.5	-22.71	not applicable*	-23.71	-2.63
P4	Max % change	not applicable	954.29 (normal to abnormal)	300 (normal to abnormal)	-37.08	-16.27	-2.17	-19.03
	Min % change	not applicable	48.57 (normal to abnormal)	WNL	-25.03	-9.04	-2.17	-15.38

P6	Max % change	not applicable	4400 (normal to abnormal)	233.3 (normal to abnormal)	-51.80	-8.06	-56.09	not applicable*
	Min % change	not applicable	WNL	WNL	-36.37	-4.84	-50.25	not applicable*
OVERALL	**Max % change**	**1935.7**	**4400**	**1450**	**-51.8**	**-19.5**	**-58.9**	**-89**
OVERALL	**Min % change**	**15**	**48.57**	**15**	**-3.1**	**-1.4**	**-0.5**	**-15.38**

The ranges of percent changes of components of the flare criteria were extracted for each patient are summarized in the table. The lowest value that is making the cut off is highlighted in blue. All other values fulfilling the flare criterion are highlighted in orange.
The lowest value that is making the cut off is highlighted in blue. All other values fulfilling the flare criterion are highlighted in orange.
*increased
**DDS change not applicable as patients had <15% during subclinical flare visits by definition
ALC, absolute lymphocyte count; CRP, C-reactive protein; D, dose reduction; DDS, daily diary score; ESR, erythrocyte sedimentation rate; HGB, hemoglobin; IFN, interferon; Max, maximum; Min, minimum; P, patient; PLT, platelets; WBC, white blood cell; WNL, within normal limits

Supplementary Table 7 Treatment decisions (steroid adjustments/baricitinib adjustments/no action) during "flare visits"

Patient	Subclinical /Clinical Flare*	Presumed cause of flare**	GC treatment action (yes/no)	Baricitinib treatment action (yes/no)***	Outcome
Post baricitinib dose reduction visits					
P1	Clinical	Intentional baricitinib dose reduction from 9 mg/day to 7 mg/day Ind: Find lowest tolerated dose RV: Stable	Yes, increased from 0.3 mg/kg/day to 0.43 mg/kg/day	No, remained on baricitinib 7 mg/day	Resolution of flare with GC increase **Flare criteria fulfilled with IFN score only → increase GC dose, temporary resolution of flare** **Flare recurred with GC dose decrease.**
P3	Clinical	Intentional baricitinib dose reduction from 8 mg/day to 6 mg/day Ind: Manage side effect, anemia RV: MDA	Yes, GC increased from 4 mg/day [0.14 mg/kg/day] to 6 mg/day [0.21 mg/kg/day] 6 weeks after baricitinib dose reduction	Yes, increased from 6 mg/day to 8 mg/day 3 months after baricitinib dose reduction	Resolution of Flare, GCs tapering **Flare criteria fulfilled → adjust baricitinib dose back to baseline** **Ability to lower CG on baricitinib 8mg/day**
P4	Subclinical	Accidental baricitinib dose reduction from 10 mg/day to 4mg/day RV: REM	No, off GCs	Yes, increased from 4 mg/day to 10 mg/day 3 days after	**Restart higher dose of baricitinib "**Resolution of Flare, off GCs" **Flare criteria fulfilled → adjust baricitinib dose back to baseline, patient remains off GCs**
P5	Clinical	Intentional baricitinib dose reduction from 10 mg/day to 9 mg/day Ind: Find lowest tolerated dose RV: REM	No, off GCs	Yes, increased from 9 mg/day to 10 mg/day one week after	Resolution of Flare, off GCs **Flare criteria fulfilled → adjust baricitinib dose back to baseline, patient remains off GCs**
P10	Clinical	Intentional baricitinib dose reduction from 12mg/day to 10mg/day Ind: Find lowest tolerated dose RV: REM	Yes, was off GCs and required 2 short courses of GCs one month and two months after dose reduction	Yes, increased from 10 mg/day to 12 mg/day one month after dose reduction	Resolution of Flare after baricitinib and GC increase, later able to wean off GCs! **Flare criteria fulfilled → adjust baricitinib dose and GC dose then able to wean GC**
P6	Clinical	Intentional baricitinib dose reduction from 6mg/day to 4 mg/day Ind: Keep viral load low RV: Stable	No, remained on GCs 3 mg/day [0.16 mg/kg/day]	No, remained on baricitinib 4 mg/day	**Persistent flare till end of study. Had 8/14 (57%) flare visits over ~2.5 yrs** **Flare criteria fulfilled → no baricitinib and no GC dose adjustment → cont' flare (see below)**

"Flare visits" in low dose period (n=17) *identified in validation phase of "flare criteria"*					
P1	Clinical	GC taper to 0.3 mg/kg/day	No	No, remained on baricitinib 7 mg/day	**Had 3/12 (25%) flare visits over 2 years**. **Flare criteria fulfilled → no baricitinib dose and no GC dose adjustment → 25% flare on GC 0.3mg/kg/d**
	Clinical	NA	No		
	Clinical	NA Ind: Lower steroid dose RV: Stable	No		
P3	Clinical	NA	No, remained on 3.5 mg/day [0.08-0.10 mg/kg/day].	No, remained on 6 mg/day	**Had 5/13 (38%) flare visits over 2.5 years.** **Flare criteria fulfilled → no adjustment of baricitinib or GC dose → 38% flare rate on GC 0.1mg/kg/d**
	Clinical	NA			
	Subclinical	NA			
	Subclinical	NA			
	Subclinical	NA Ind: Manage side effect, anemia RV: MDA)			
	Clinical	GC taper to 0.06 mg/kg/day	No	No, remained on baricitinib 7 mg/day	**Had 2/6 (33%) flare visits over 13 months.** **Flare criteria fulfilled → higher baricitinib dose (7mg/d) allowed further GC reduction to 0.06mg/kg/day.**
	Subclinical	NA Ind: Manage side effect, anemia RV: MDA)	No, remained on 3 mg/day [0.06 mg/kg/day]		
P6	Subclinical	NA	No, remained on 2.5-3 mg/day [0.10-0.16 mg/kg/day]	No, remained on baricitinib 4 mg/day	**Had 8/14 (57%) flare visits over ~2.5 yrs** **Flare criteria fulfilled → baricitinib dose (4 mg/d and GC 0.16mg/kg/d with continued intermittent flares**
	Clinical	NA			
	Clinical	NA			
	Subclinical	NA			
	Clinical	NA			
	Subclinical	NA			
	Subclinical	NA Ind: Keep viral load low Parental worries. RV: Stable			
"Flare visits" in high dose period (n=12) *identified in validation phase of "flare criteria"*					
P1	Clinical	GC taper to 0.35 mg/kg/day	Yes, increased from 0.35 mg/kg/day to 0.38 mg/kg/day	No, remained on baricitinib 8 mg/day	Had 2/3 (66%) flare visits, on GCs at ~0.35 mg/kg/day over 10 months **Flare criteria fulfilled → no baricitinib and no GC change →ongoing disease activity**
	Clinical	GCs tapering to 0.3mg/kg/day Ind: Lower steroid dose RV: Stable	No	**Yes, increased to 9 mg/day**	**Had 0/3 (0%) flare visits, GCs tapering to 0.3 mg/kg/day over 8 months** **Flare criteria fulfilled → higher baricitinib dose (9mg/d) GC 0.3 mg/kg/day optimally protected the patient.**
	Clinical	NA	No	No, remained on baricitinib 8 mg/day	Had 3/8 (38%,) flare visits over 2 years and was able to taper GC to 0.14 mg/kg/day. **Flare criteria fulfilled → baricitinib dose (8mg/d) allowed further GC reduction to 0.14 mg/kg/day but with overall poorer control than at the 9 mg/day dose.**
	Subclinical	NA	No		
	Clinical	GC taper:6.5 mg/day 0.23 mg/ kg/day to 5 mg/day 0.13 mg/ kg/day] Ind: Lower steroid dose	No		

		RV: Stable			
	Clinical	NA	**No, remained on ~0.13 mg/kg/day**	**No, remained on 9 mg/day**	Had 1/4 (25%) over 9 months, on GCs 0.14mg/kg/day, no change from prior visits **Flare criteria fulfilled → higher baricitinib dose (9mg/d) on GC dose 0.14 mg/kg/day.**
P4	Subclinical	NA	No, remained on baricitinib 8mg/day	Had 2/21 (9%) flare visits over 5 years, off GCs (*adolescent-adult transition*)	Had 2/21 (9%) flare visits over 5 years. (*adolescent-adult transition*) **Flare criteria fulfilled → with baricitinib taper to (8mg/d), no GC.**
	Subclinical	NA Ind: Find lowest tolerated dose RV: REM			
P5	Clinical	NA	No, off GCs	No, remained on baricitinib 10 mg/day	Had 3/17 (18%) flare visits over 4.5 years, off GCs
	Clinical	NA			
	Clinical	NA Ind: Find lowest tolerated dose RV: REM			
P10	Clinical	NA	No, off GCs	No, remained on baricitinib 12 mg/day	Had 2/11 (18%) flare visits off GCs (*adolescent-adult transition*)
	Clinical	NA Ind: Find lowest tolerated dose RV: REM	No, off GCs		
Additional high-dose Visits					
P3	Patient had 12 high-dose visits over ~2.5 years and did not have clinical or subclinical flare. During these high-dose visits, patient was on baricitinib 10 mg/day for 3 months and on 8 mg/day for ~2.2 years. Overall, achieved GC tapering down to 0.09 mg/kg/day				Flare rate 0%, GCs tapering
P6	Patient had 3 high-dose (on baricitinib 6 mg/day) visits over 6.8 months and did not have clinical or subclinical flare. Achieved GC tapering from 0.46 mg/kg/day to 0.16 mg/kg/day				Flare rate 0%, GC tapering

*all visits that were identified by fulfilling the proposed flare criteria (clinical and subclinical flares) in the validation phase are listed here.
** in column presumed cause of flare, we added the reason for the presumed flare i.e glucocorticoid taper, baricitinib dose reduction, other. We also determined the level of disease control the patient had prior to the flare at the reference visit (RV): remission (REM) meaning DDS<0.15, normal CRP and off steroids (P4, P5, P10) , minimal disease activity (MDA), DDS<0.15, normal CRP, prednisone equivalent <0.15mg/kg/day (P3) and stable for patient who normalized CRP but had still elevated DDS and were on higher doses of steroids (P1, P6, P7). See supplementary table 7. P7 was on high doses of steroids 0.8 mg/kg/day and could not be tapered. P7 was not included in the validation of the criteria.
***all baricitinib dose increases were within the dose range of the provided dosing table (Kim at al. 2018)
GC, glucocorticoid; Ind, indication; MDA: minimal disease activity; NA, not available; P, patient; REM, remission; RV, reference visit.

Actual clinical scenarios observed:

Scenario 1: In patient P4 who had subclinical flares only and in patients P5 and P10 who had clinical flares after fulfilling remission criteria off GC, the baricitinib dose was adjusted after a baricitinib dose reduction during "low-dose visits". The flare resolved in P4 and P5 by adjusting the baricitinib dose back to baseline. In P10, two short courses of GCs were required in addition to a baricitinib dose adjustment to achieve remission again.

However, flares identified in the validation period during the "high dose visits" did not result in GC or baricitinib changes. On subsequent visits P4, P5 and P10 fulfilled flare criteria on 9%, 18% and 18% of visits respectively.

Scenario 2: Post flare P1 (S, stable disease) remained on baricitinib 7 mg/day and GC doses between 0.23-0.30 mg/kg/day. Over the next ~2 years he had 3 clinical flare visits out of 12 low-dose visits (25% flare visits) and was unable to wean GC. The baricitinib dose was adjusted to 8 mg/day and GCs could be tapered to 0.14 mg/kg/day, however he had 2 clinical and 1 subclinical flare visits out of 8 high-dose visits (38% flare visits) over 2 years. Eventually the baricitinib dose was increased to 9 mg/day, and he had 1 clinical flare visit out of 4 high-dose visits (25% flare visits) and remained on GCs 0.14 mg/kg/day.

In patients P3 (MDA) and P6 (S, stable disease) the baricitinib dose reduction without subsequent dose adjustment resulted in 38% and 57% of subsequent visits fulfilling "flare criteria" respectively during a period of ~2.5 years. In P3 the baricitinib dose was eventually increased to 8 mg/day which allowed a GC taper to doses below 0.15mg/kg/day (criteria for MDA) with no subsequent clinical or subclinical flares (flare rate 0%). In P6 the family elected to stay on a lower baricitinib dose and not adjust baricitinib or GC dose.

Suggestion: The proposed flare criteria can be used to manage patients with CANDLE/PRAAS in remission or with MDA. The scenarios above illustrate their use in finetuning treatment and adjusting steroid doses to the lowest dose possible in patients with MDA. In patients who achieved remission, the "flare rates" may help in quantifying disease control long-term and to better characterize the "level of disease control" that can be achieved on treatment with janus kinase inhibitors.

Proposed use of criteria for monitoring CANDLE/PRAAS patients who are in clinical remission (P4, P5, P10) or have minimal disease activity (P3), clinical scenarios:

1. Baricitinib dose reductions to determine the lowest dose tolerated with the goal to:
    a. Keep BK viral load in blood as low as possible but below log 4 copy/ml (10,000 copies/ml) at all times, consistent with recommendations for BK viral load monitoring for kidney transplant recipients. [6 7] **P3** (MDA)**)**
    b. Manage side effects such as anemia **(P3)** (MDA).
    c. Find lowest tolerated dose in patients in remission or with minimal disease activity **(P3** (MDA) **P4** (REM), **P5** (REM), **P10** (REM)**)**

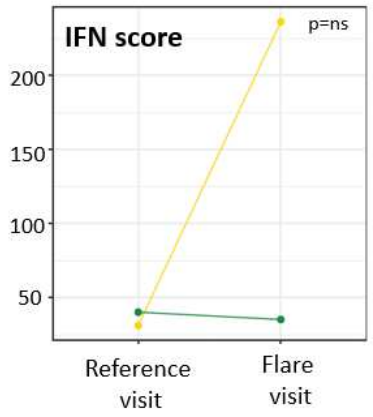
2. Lower steroids doses in patients with MDA

The use of the criteria in patients who <u>are not</u> in clinical remission or fulfill criteria for MDA, but have stable disease needs to be evaluated prospectively in a larger cohort. Clinical scenarios (P1, P6) where they may be useful include:

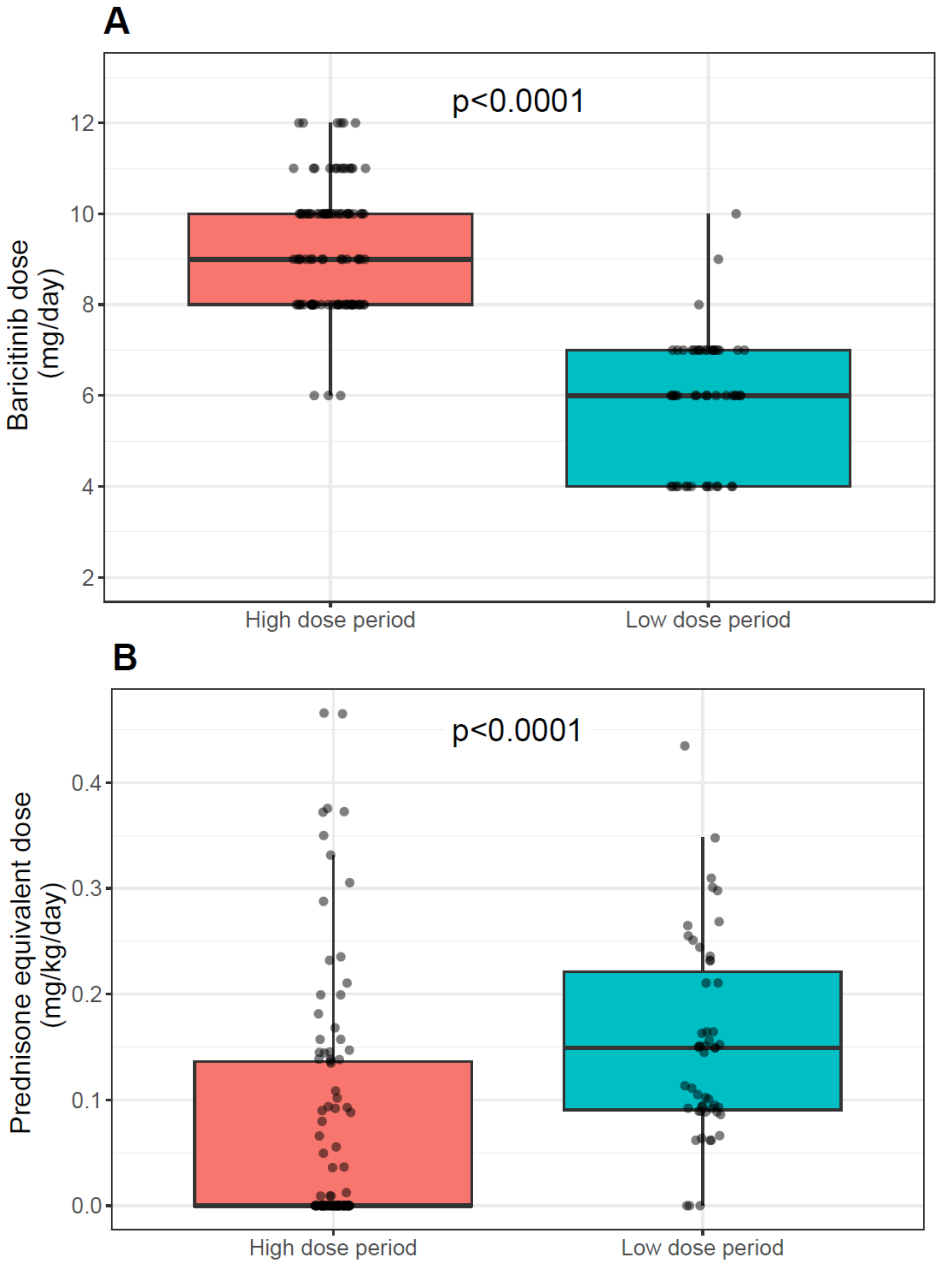
1. Baricitinib dose reductions to:
   a. Keep BK viral load in blood as low as possible but below log 4 copy/ml (10,000 copies/ml) at all times, consistent with recommendations for BK load monitoring for kidney transplant recipients. [6 7] **(P1** (S), **P6** (S)**)**
   b. Manage side effects such as anemia.
2. Lower steroid doses in patients on GC doses, that are too high to achieve catch up growth (>0.15mg/kg/day) **(P1** (S), **P6** (S)**)**

The flare criteria are not useful for patients who have not achieved disease control.
P7 (active, high dose of prednisone, excluded) never achieved disease control. Baricitinib was withdrawn due to BK nephrotoxicity.

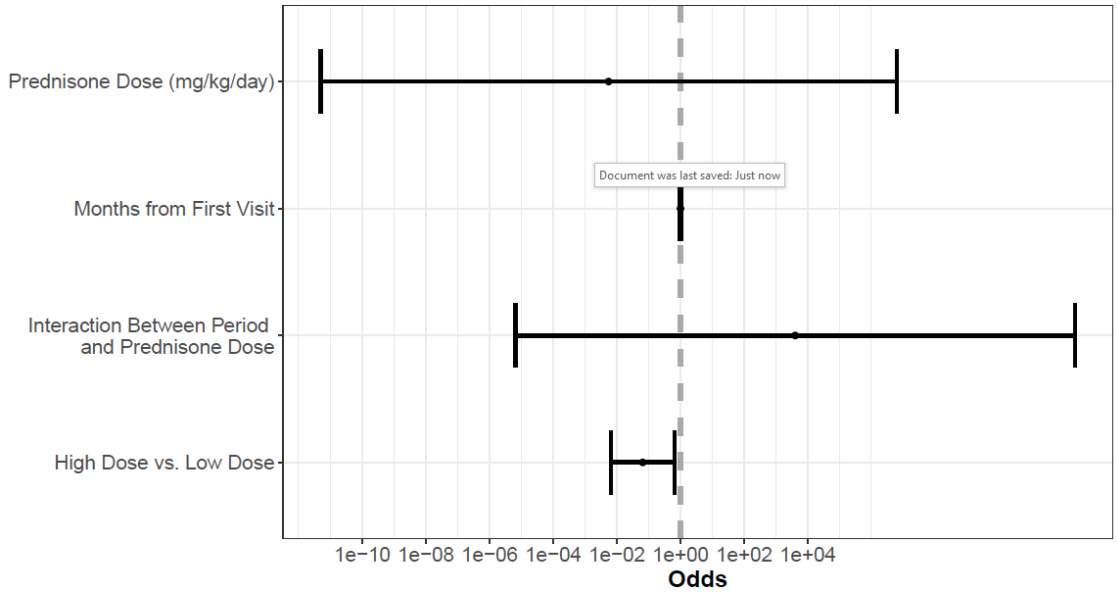
III. Supplementary Figures



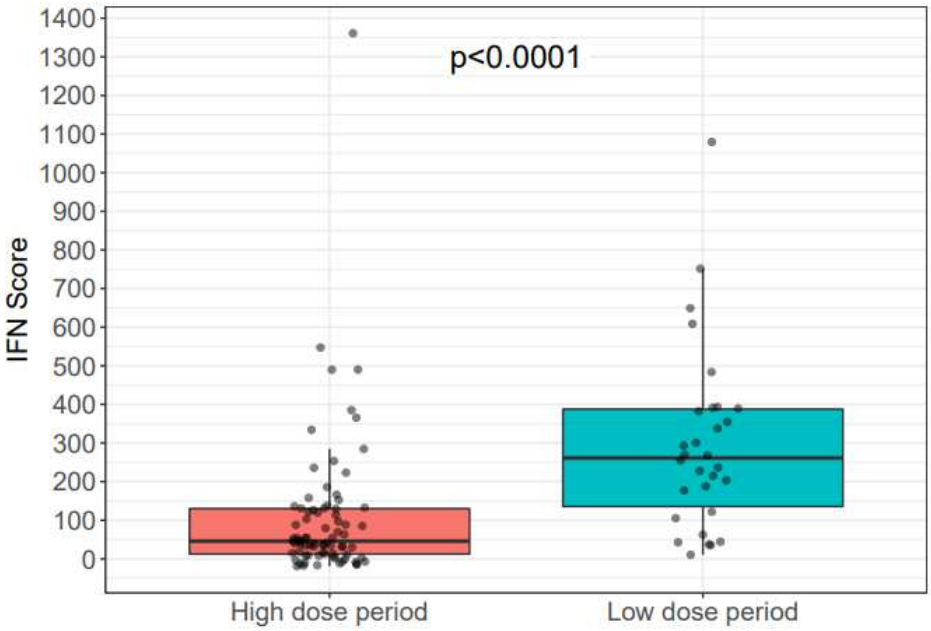
Supplementary Figure 1: Acute IFN score change with baricitinib dose reduction. This figure depicts comparison of the reference visit (=last visit before baricitinib dose reduction) with flare visit (=the first visit after dose reduction) for IFN score in patient 1 (yellow line) and patient 4 (green line). Patient 4 achieved remission nine months prior to baricitinib dose reduction and was in long term remission at the time of dose reduction. A two-sided nonparametric Wilcoxon signed rank test with uncorrected p-values were used to underscore the descriptive representation. IFN, interferon.



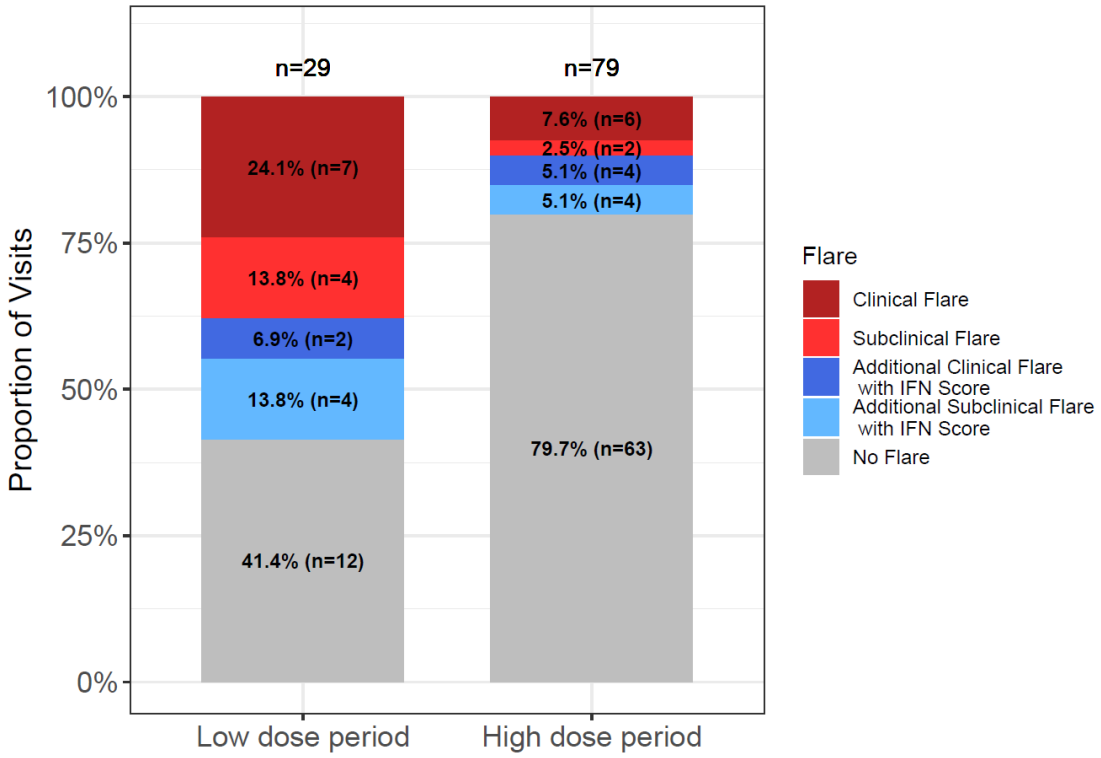
Supplementary Figure 2: Baricitinib and prednisone equivalent dose high baricitinib dose period versus low baricitinib dose period. A. The baricitinib dose was significantly higher in the high dose period compared to low dose period (median [IQR]: 9.00 [2.00] mg/day and 6.00 [0] mg/day respectively, p<0.0001). B. The prednisone equivalent dose was significantly lower in the high dose period compared to the low dose period (median [IQR]: 0.00 [0.136] mg/kg/day and 0.149 [0.13] mg/kg/day respectively, p<0.0001)



Supplementary Figure 3: Logistic regression analysis adjusting for prednisone equivalent dose. A total of 153 visits were assessed using generalized estimating equations with a correction for small sample (saws citation) given multiple visits are present per participant. Adjusting for prednisone equivalent dose, higher odds of a flare in the low baricitinib dose period than in the high baricitinib dose period are found (p=0.032). There are no significant associations with the months from first visit and prednisone. An interaction term between period (low vs high dose period) and mean prednisone dose to determine if the association between period and flare depends on the level of prednisone dose. There is not significant interaction between period and prednisone dose.



Supplementary Figure 4: Interferon (IFN) score during high baricitinib dose period versus low baricitinib dose period. A total of 153 visits from six patients were identified during the low dose and high dose baricitinib periods. Of 153 visits, the IFN score was measured in 108 visits (n=29 low dose visits and n=79 high dose visits). The median [IQR] IFN score was 45.93 [117.78] in the high dose period and 254.46 [267.56] in low dose period. Difference between median IFN score in low dose versus high dose period is significant (p<0.0001). A two-sided Wilcoxon Rank Sum test was used for comparison.



Supplementary Figure 5: Comparison of proportion of disease flares in baricitinib low dose (n=29) and high dose (n=79) visits when adding IFN score criterion to the flare criteria. This sub analysis compares the flare rate when using the flare criteria without the IFN score (red) and with the IFN score (blue). A total of 108 visits with available IFN score could be included in the analysis, of these 79/108 visits and low dose period consists of 29/108 visits. The proportion of visits when patients fulfilled flare criteria during the low dose and high dose period was calculated separately for flare criteria without and with the IFN score using a two-sided chi-squared test of homogeneity. Proportion of visits that patients fulfilled the flare criteria during the low dose period (37.93%, n=11/29) is significantly higher ($p<0.001$) than during the high dose period (10.13%, n=8/79). When adding the IFN score criterion to the flare criteria, we identified six additional clinical flares and eight additional subclinical flares, four in low-dose visits and four in the high-dose visits. The proportion of visits that patients fulfill flare criteria increased from 37.93% to 58.62% (n=17/29) during the low dose period and from 10.13% to 20.25% (n=16/79) during the high dose period. The difference is significant ($p<0.001$).

Supplementary References

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