Rapid policy statement

Ruxolitinib for acute graft versus host disease (RPS 2009)

23 November 2020, Version 1.1

Summary

In response to the public health emergency posed by coronavirus disease 2019 (COVID-19), NHS England and NHS Improvement have established a rapid policy development process to aid clinicians in offering best care and advice to patients with or at risk of COVID-19. This document sets out the recommendations for the use of ruxolitinib in graft versus host disease (GvHD) in the context of COVID-19.

Plain language summary

Allogeneic stem cell transplantation involves taking stem cells from a healthy person (the donor) and putting them into the patient's body after high-intensity chemotherapy or radiation. Stem cells are the body's raw materials — cells from which all other cells with specialized functions are generated. The donated stem cells can come from either a related or an unrelated donor. Allogeneic stem cell transplantation is a treatment used for some patients with blood cancers or other bone marrow diseases. This is a very intensive therapy with serious possible side effects. In some cases, the transplanted cells recognise the recipient's cells as "foreign" and attack them. This is known as graft versus host disease (GvHD). GvHD can occur within a few months of the transplant or develop several months or occasionally a year or 2 later. The condition is usually mild, but can sometimes be life-threatening. GvHD can be treated with medications that suppress your immune system and stop the transplanted stem cells attacking the rest of your body. This policy provides access to a drug called ruxolitinib. Recent evidence has shown that this can be effective for treating GvHD in patients who have not responded to steroids. It is given as a tablet at home will reduce the need for patients to attend hospital so frequently and reduce the risk of catching COVID-19.
The condition

GvHD is a complication of allogeneic haematopoietic stem cell transplantation (allo-HSCT) and can be serious and life-threatening. GvHD can affect the skin, mouth, eyes, lung, liver and gut. There are two types of GvHD: acute and chronic. Acute GvHD (aGvHD) generally starts within 100 days of transplant and chronic GvHD (cGvHD) 100 days after transplant; however, signs of acute and chronic GVHD may occur outside of these designated periods. Both types can present with mild to severe symptoms. First-line treatments include topical therapies, systemic corticosteroids or calcineurin inhibitors. For patients with corticosteroid-refractory GvHD, second-line or subsequent therapy is guided by grade and clinical presentation of GvHD and a number of treatment options exist. NHS England currently commissions extracorporeal Photopheresis (ECP) for aGvHD and ECP, pentostatin, rituximab and imatinib for cGvHD (NHS England: 16069/P).

At present, access to ECP for aGvHD in the UK is generally limited to those centres where ECP is available on site as patients are often too unwell to travel for treatment. NHS England and NHS Improvement concluded that there is enough evidence to consider making the following treatment available patients with acute GvHD – ECP.

In 2018 there were 1,304 adult allogeneic transplants (British Society for Blood and Marrow Transplantation). The incidence of the most severe grade III and IV categories of aGvHD in adults requiring second or subsequent lines of therapy is 7% (399 patients, 2013 to 2017 cohort). The rate of extensive cGvHD in adult allograft recipients is 6% (318 patients, 2013 to 2017 cohort); these patients will require second or subsequent lines of therapy (British Society for Blood and Marrow Transplantation).

Intervention

The Janus kinase (JAK) and signal transducers and activators of transcription (STAT) signalling pathways are activated in GvHD. Ruxolitinib is a selective inhibitor of JAK1 and JAK2 and available as a tablet that can be self-administered at home. There is emerging evidence of efficacy in aGvHD and some evidence in c GvHD. Ruxolitinib does not have a European Medicines Agency (EMA) licence for GvHD but does have Food Drug Administration (FDA) approval for acute GvHD.

Clinical problem

The most common treatment option for corticosteroid-refractory GvHD is ECP. This procedure involves being attached to a machine that removes blood through a cannula, separates the white cells, exposes them to UV light before returning the blood into a vein. Treatment can take 1–2 hours at a time and patients usually attend multiple times a week. Treatment duration depends on response but in some cases can last 12–18 months or longer. Due to COVID-19
there is an urgent need to avoid hospitalisation in high-risk patients. Ruxolitinib provides an alternative treatment option which can be taken at home without the need to attend hospital unless adverse events occur.

**Evidence summary**
Three papers were reviewed by Solutions for Public Health and can be found in Appendix 1.

**Recommendations and implications for clinical practice**

**Implementation**

**Inclusion criteria**

Ruxolitinib (10 mg oral twice daily\(^1\)) is made available as an option for patients who are post pubescent and meet the following criteria:

a) patient presents with continued or relapsed clinical features of aGvHD (eg maculopapular rash, persistent nausea and/or emesis, abdominal cramps with diarrhoea, and a rising serum bilirubin concentration) as determined by clinical examination or biopsy where disease constellation is not clear; and

b) refractory to corticosteroids (as defined by local policy); and

c) adequate bone marrow reserve defined as absolute neutrophil count >1000 cells/mm\(^3\) and a platelet count of at least 20,000 cells/mm\(^3\) within 48 hours before initiation of therapy; and

d) no more than one treatment for corticosteroid-refractory aGvHD (not including calcineurin inhibitors, sirolimus or mycophenolate mofetil). (Note: Patients do **not** need to have failed ECP to be eligible for ruxolitinib.)

The multidisciplinary team should include a paediatrician and/or a paediatric pharmacist where treatment is for a child.

**Exclusion criteria**

a) Active uncontrolled infection.

b) Prior treatment with a JAK inhibitor.

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\(^1\) Dose adjustments may need to be made based on efficacy and adverse events.
Stopping criteria

Patients must be reviewed at day 28 of treatment with ruxolitinib; if no response is observed then ruxolitinib should be discontinued. If there is partial response to treatment, patients should be reviewed again at day 56.

Monitoring

Monitoring during the COVID environment should be decided locally based on the risk to the individual and where appropriate in accordance with NICE COVID-19 rapid guideline: haematopoietic stem cell transplantation (www.nice.org.uk/guidance/ng164).

Governance

Recommendations for data collection

All providers of HSCT must be Joint Accreditation Committee-ISCT and EBMT (JACIE) accredited. NHS England will commission from specialised HSCT centres, which will provide oversight of diagnosis of GvHD and initiation of ruxolitinib. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. The governance arrangements are described in detail in the bone and marrow transplant (BMT) service specifications for adults (B04/S/a) and children (B04/S/b).

Patient data is to be mandatorily collected as part of an annual audit to monitor efficacy and safety according to agreed outcomes. The audit should report on the following:

- demographics
- previous GvHD treatments
- date of transplant
- type of transplant (eg full intensity, reduced intensity, T-cell deplete)
- underlying disease
- grade of GvHD when starting ruxolitinib (grade I–IV as per the 1994 consensus criteria (Przepiorka et al 1995)
- response at day 28 (eg complete resolution or partial response improvement by at least one grade)
- treatment cessation due to drug toxicity.

Effective from

Policy will be in effect from publication.
Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England’s values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Policy review date

This is a rapid policy statement developed as part of the emergency response to COVID-19. The usual policy development process has been condensed and abridged. This document will be reviewed prior to April 2021.
### Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tr>
<td><strong>Allogeneic haematopoietic stem cell transplant (allo-HSCT)</strong></td>
<td>Allo-HSCT is used to treat carefully selected patients with a range of malignant and non-malignant haematological disorders, and other specific disorders of the immune system. It involves replacing a patient’s bone marrow stem cells following high dose therapy with stem cells from a donor.</td>
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<td><strong>Corticosteroid</strong></td>
<td>Man-made version of hormones normally produced by the body. When taken in doses higher than the amount your body normally produces, steroids reduce redness and swelling (inflammation). This can help with inflammatory conditions such as asthma, eczema and vasculitis. Steroids also reduce the activity of the immune system, which is the body's natural defence against illness and infection.</td>
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<td><strong>Extracorporeal photopheresis (ECP)</strong></td>
<td>A treatment option for acute and chronic GvHD. This procedure involves being attached to a machine that removes blood through a cannula, separates the white cells, exposes them to UV light to destroy the white blood cells that cause GvHD before returning the blood into a vein. Treatment can take 1–2 hours at a time and patients usually attend multiple times a week. Treatment duration depends on response but in some cases can last 12–18 months or longer.</td>
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<td><strong>Graft versus host disease</strong></td>
<td>GvHD is a common complication of allo-HSCT which is a major cause of post-transplant mortality and morbidity. It is caused by immune incompatibility between the donor and recipient tissues. The graft cells recognise the recipient tissues as foreign, and mount an immune response against them. Acute GvHD (aGvHD) is characterised by a generalised patchy skin rash, sickness, weight loss, loss of appetite, watery diarrhoea, severe abdominal pain, bloody diarrhoea and jaundice. aGvHD is graded in severity from I (mild) through II (moderate), III (severe) to IV (very severe) according to the modified Seattle Glucksberg criteria. The grade correlates to survival prognosis with 5-year survival of 25% for grade e and 5% for grade IV disease. (Gratwohl et al 1995; Cahn et al 2005). Chronic GvHD (cGvHD) may present with a wider range of symptoms and affects almost any organ, but typically includes symptoms such as alopecia (hair loss), skin</td>
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thickening and severe rash/erythema of the skin, nail loss, dry mouth and oral lesions, dry eyes, sore muscles and joints, raised liver enzymes, scarring of lung tissue with reduced lung function, pericarditis, and loss of blood cells (red, white and platelets). cGvHD is diagnosed and categorised according to the National Institutes of Health (NIH) consensus criteria (Jagasia et al. 2014). cGvHD can cause a great degree of morbidity with loss of health and an increased risk of infection. It can be life-limiting.

References


Appendix 1

Evidence summary

Three papers were presented for review by NHS England and NHS Improvement. Paper 1 is an international multicentre, open label, phase 3 randomised controlled trial comparing ruxolitinib with control treatment. Paper 2 is a prospective, US multicentre, open-label, single cohort phase 2 trial of ruxolitinib. Paper 3 is an international retrospective multicentre survey of outcomes for patients who had received ruxolitinib.


This randomised controlled, open label, phase 3 trial compared the efficacy and safety of oral ruxolitinib to a control. 309 patients aged ≥12 years (median age 54, range 12–73 years) who had glucocorticoid-refractory aGvHD after allo-HSCT were recruited between April 2017 and May 2019 from 105 treatment centres across 22 countries (including three centres in the UK). Randomisation to treatment with ruxolitinib or control was stratified according to the baseline grade of aGvHD (grade II vs III vs IV) in a 1:1 ratio.

154 patients were assigned to receive oral ruxolitinib (10 mg twice daily); 155 patients were assigned to receive the investigators choice of therapy² (the control) for up to 24 weeks. 49/155 patients (32%) crossed over to receive ruxolitinib on or after day 28. Standard supportive therapy (including growth factors, anti-infective medication, transfusion support and other standard supportive care measures) was allowed in both treatment groups in addition to the continued use of calcineurin inhibitors and glucocorticoids.

At the data cut-off date, the median follow-up was 5.04 months (range 0.03–to 24.02) among patients in the ruxolitinib group and 3.58 months (range 0.03–23.62) among those in the control group.


This prospective, multicentre, open-label, single cohort phase 2 trial evaluated the efficacy and safety of oral ruxolitinib in 71 patients aged ≥12 years (median age 58, range 18–73 years) with grades II to IV SR aGvHD after allo-HSCT for haematological malignancies. The primary endpoint of the study was overall response rate (ORR) at day 28.

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² Anti-thymocyte globulin, ECP, mesenchymal stromal cells, low-dose methotrexate, mycophenolate mofetil, mammalian target of rapamycin (mTOR) inhibitor (everolimus or sirolimus), etanercept or infliximab.
Patients recruited between 27 December 2016 and 2 July 2018 from 26 medical centres in the USA, received ruxolitinib 5 mg twice daily (with an option to increase to 10 mg twice daily in the absence of cytopaenia) plus corticosteroids until treatment failure, unacceptable toxicity or death. Treatment continued until treatment failure, unacceptable toxicity or death. All patients received concomitant anti-infective prophylaxis.

At the time of the analysis, 30 patients (42.3%) remained on study and 11 (15.5%) were receiving ruxolitinib. The median follow-up interval was 156.0 days (range 9–518). The median duration of ruxolitinib treatment for all patients was 46 days (range 4 to 473), and the median average total daily dose was 10.3 mg/day (range 5 to 20).


This retrospective multicentre survey of outcomes for patients who had received ruxolitinib for grade III or IV SR-aGvHD reported safety and response data. Patients were recruited between January 2012 and April 2015 from 19 stem cell transplant centres in Europe (none of these centres was in the UK) and the USA.

54 patients (median age 51 years, range 21–75) with grade III or IV aGvHD were treated with oral ruxolitinib 5–10 mg twice daily as an add-on immunosuppression therapy. 34 patients (63%) had multiple organ involvement and 39 patients (72.2%) were beyond second-line treatment for aGvHD. The median number of previous aGvHD-therapies was three (range 1–7). The duration of treatment was not stated. The median follow-up time was 26.5 weeks (range 3–106).

**Effectiveness**

**Overall response**

Zeiser et al 2020 reported that overall response at day 28 was significantly higher in the ruxolitinib group than in the control group (62% (96/154 patients) vs 39% (61/155 patients); odds ratio 2.64, 95% CI 1.65–4.22, p<0.001). The best overall response up to day 28 was 82% (126 patients) in the ruxolitinib group and 61% (94 patients) in the control group (odds ratio 3.07, 95% CI 1.80–5.25, p-value not reported). The proportion of patients who achieved a complete response (CR) was higher in those treated with ruxolitinib than control: 34% (53 patients) vs 19% (30 patients) (significance not reported).

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3 Defined as the proportion of patients who had a CR or PR as compared with baseline organ staging without the use of additional systemic therapy for aGvHD.

4 Defined as the percentage of patients who had a CR or PR at any time up to and including day 28 and before the start of additional systemic therapy for aGvHD.
In Jagasia et al 2020, the day 28 ORR\(^5\) was 54.9\% (39/71 patients, 95\% CI 42.7–66.8). This included 19 patients (26.8\%) with a CR, seven (9.9\%) with a very good partial response (VGPR) and 13 (18.3\%) with a PR. Responses were observed across skin (61.1\%), upper (45.5\%) and lower (46.0\%) gastrointestinal tract, and liver (26.7\%). The median time to first response was 7 days (range 6–49); 43 patients (60.6\%) had first response on or before the day 14 visit.

The best ORR at any time was 73.2\% (95\% CI 61.4–83.1, CR 56.3\%), which included nine patients (12.7\%) who had a response (two CR, one VGPR, six PR) before day 28 but did not respond at the day 28 visit, and four patients (5.6\%) who responded after day 28 (one CR, three PR).

In Zeiser et al 2015, the ORR\(^6\) was 81.5\% (44/54) including 25 CRs (46.3\%). A CR to ruxolitinib was defined as the absence of any symptoms related to GvHD. A PR was defined as the improvement of at least one stage in the severity of aGvHD in one organ without deterioration in any other organ. A response had to last for at least 3 weeks. The median time to response was 1.5 weeks (range 1–11) after initiation of ruxolitinib treatment.

**Overall response and GvHD grade**

Zeiser et al 2020 reported that the proportion of patients with grade II aGvHD at baseline who had a response to ruxolitinib compared to control was 75\% (40/53 patients) vs 51\% (27/53 patients). A lower proportion of patients with grade III aGvHD at baseline responded to either ruxolitinib or control (56\% (40/71 patients) vs 38\% (27/72 patients)). Although fewer patients with grade IV aGvHD responded to treatment, the authors reported that this group had the greatest capacity to benefit from treatment with ruxolitinib compared to control (53\% (16/30 patients) vs 23\% (7/30 patients), odds ratio 3.76, 95\% CI 1.24–11.38).

Jagasia et al 2020 also reported that day 28 response was associated with aGvHD grade at enrolment. Of the 48 patients with grade III/IV aGvHD, 11 (22.9\%) achieved a CR or VGPR at day 28. In a post-hoc model-based analysis, grade II vs grade III/IV aGvHD was significantly associated with day 28 response (odds ratio 0.15, 95\% CI 0.04–0.55, \(p=0.0042\)). Patients with grade II and grade III/IV aGvHD at enrolment with skin involvement had day 28 ORRs of 88.2\% and 36.8\% respectively. Patients with grade II and grade III/IV aGVHD without skin involvement had day 28 ORRs of 66.7\% and 44.8\% respectively.

**Durable response**

\(^5\) Defined as the proportion of patients demonstrating a CR, VGPR, or PR.

\(^6\) Defined as proportion of patients achieving best response (CR or PR) at any time after starting treatment with ruxolitinib, with follow-up censored at the onset of any subsequent systemic immunosuppressive therapy.
Zeiser et al 2020 reported durable overall response at day 56. This was significantly higher in the ruxolitinib group than in the control group (40% (61 patients) vs 22% (34 patients); odds ratio 2.38, 5% CI 1.43–3.94, p<0.001).

Jagasia et al 2020 reported the duration of response (DOR) defined as the time from first response to GvHD progression or death, calculated once all patients reached 6 months. The median DOR response at 6 months was 345 days (lower limit, 159 days). The median DOR at 6 months for patients with a response at any time was also 345 days (lower limit, 106 days).

**Cumulative incidence of loss of response**

Zeiser et al 2020 reported the estimated cumulative incidence of loss of response at 6 months was 10% (95% CI 4–17) in the ruxolitinib group and 39% (95% CI 26–52) in the control group.

Zeiser et al 2015 reported relapses in aGvHD in 6.8% (3/44) of ruxolitinib-responsive patients.

**Overall survival**

Zeiser et al 2020 reported the median overall survival (OS) for patients treated with ruxolitinib (n=154) compared to control (n=155) treatment: 11.1 months vs 6.5 months (hazard ratio (HR) for death 0.83, 95% CI 0.60–1.15).

Jagasia et al 2020 reported the overall survival rate at 6 months (51.0%, 95% CI 38.7–62.1) and 12 months (42.6%, 95% CI 30.0–54.6) for all 71 patients who had been treated with ruxolitinib. The median OS was 7.6 months (95% CI 3.1: not evaluable).

Patients who had responded to ruxolitinib by day 28 had better outcomes. Response status was an independent predictor of OS (HR 0.40, 95% CI 0.26–0.61, p<0.0001).

- OS probability was 81.8% for 11 of the 48 patients with grade III/IV aGvHD
- OS was greater for day 28 responders compared with non-responders (p<0.0001).
- OS was greater for day 28 responders compared or other responders (p=0.0016).
- The probability that day 28 responders were alive at 6 and 12 months was 73.2% (95% CI 55.9–84.6) and 66.2% (95% CI 47.8–79.4) respectively.

Model-based analysis suggested that reduced OS was associated with:

- grade III/IV aGvHD: p=0.0076

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7 *defined* as the proportion of patients in each treatment group who had response at day 28 that was maintained at day 56

8 Time from randomisation to death due to any cause.
• duration of prior corticosteroid exposure: HR 1.01, 95% CI 1.00–1.02, p=0.0015.

Zeiser et al 2015 estimated that 79% (95% CI 67.3–90.7) of patients receiving ruxolitinib for aGvHD would be alive at 6 months. The median follow-up time was 26.5 weeks (range 3–106).

**Failure-free survival**

Failure-free survival was defined by Zeiser et al 2020 as time from randomisation to relapse or progression of haematological disease, non–relapse-related death or the addition of new systemic therapy for aGvHD; the competing risk was the onset of cGvHD.

Zeiser et al 2020 reported significantly longer median failure-free survival in the ruxolitinib group than in the control group (5.0 months vs 1.0 month, HR 0.46, 95% CI 0.35–0.60).

At 1 month, the cumulative incidence of events contributing to failure-free survival was lower in the ruxolitinib group than in the control group (18% vs 49%). At 18 months, for patients treated with ruxolitinib vs control, the cumulative incidence of:

- events contributing to failure-free survival was 61% vs 82%
- cancer relapse or progression for patients was 13% vs 19%
- non–relapse-related death was 49% vs 51%.

Jagasia et al 2020 reported cancer relapse in 5.6% (4/71)) patients treated with ruxolitinib (acute myeloid leukaemia, n=2 (both fatal)); myelodysplastic syndrome, n=1; plasma cell leukaemia, n=1 (fatal)). Two relapses occurred on the day of ruxolitinib discontinuation; two occurred 34 and 99 days from the last dose of ruxolitinib.

Jagasia et al 2020 also reported non-relapse mortality (NRM). 35/71 (49.3%) patients treated with ruxolitinib died of causes other than malignancy relapse, including 10 patients who died within the first 28 days. The 6- and 12-month cumulative incidence rates for NRM were 44.4% (95% CI 32.5–55.7) and 52.9% (95% CI 39.6–64.5) respectively for all patients and were lower for responders. Among the 11 patients with CR or VGPR, NRM cumulative incidence rate was 9.1% at both 6 and 12 months. Response status was an independent predictor of NRM (HR 0.442, 95% CI 0.29–0.69, p=0.0003).

Model-based analysis suggested that increased NRM was significantly associated with:

- aGvHD grade III/IV: HR 0.252, 95% CI 0.11–0.58, p=0.0013
- longer prior corticosteroid exposure: HR 1.01, 95% CI 1.01–1.02, p=0.0001.

Zeiser et al 2015 reported relapse of the underlying malignancy in 9.3% (5/54) of patients.
Development of cGvHD

Jagasia et al 2020 reported a median follow-up of 323 days (range 57–518) for surviving patients; four developed cGvHD after discontinuation of ruxolitinib (on study days 55, 115, 156 and 347).

Corticosteroid use

Zeiser et al 2020 reported that by day 56, 32/154 patients (21%) treated with ruxolitinib had discontinued glucocorticoids compared to 21/155 (14%) in the control group.

In Jagasia et al 2020 (n=71), the median corticosteroid dose at enrolment was 156.3 mg/day (50.0–300.0). By day 28, the median corticosteroid dose was 62.5 mg/day; 55.8% (24/43) of patients receiving ruxolitinib at day 28 had a 50% or more reduction from baseline corticosteroid dose.
Safety

Zeiser et al 2020 reported that adverse events occurred in most patients in both the ruxolitinib and control treatment groups (95% and 93% respectively) including serious adverse events up to day 28 in 57 patients (38%) who had received ruxolitinib and in 51 patients (34%) who had received control therapy.

Jagasia et al 2020 reported that all the 71 patients treated with ruxolitinib had at least one treatment-emergent adverse event (TEAE); 69 patients (97.2%) had a grade III or higher\(^9\) TEAE.

Zeiser et al 2015 reported adverse events in 48/54 (88.9%) patients with aGvHD treated with ruxolitinib.

Death

Zeiser et al 2020 reported 149 deaths by the data cut-off date: 72/154 patients (47%) in the ruxolitinib group and 77/155 patients (51%) in the control group. 43 (28%) and 36 (24%) deaths respectively occurred during the randomised treatment period (median duration of randomised treatment period was 63 days and 29 days in the ruxolitinib and control groups respectively). aGvHD was the cause of death in 34 patients in the ruxolitinib group and in 37 patients in the control group. The most commonly reported causes of death were underlying disease progression including neoplasms (in eight patients in the ruxolitinib group and eight in the control group), multiple organ dysfunction syndrome (in three and one respectively), sepsis (in four and three respectively) and septic shock (in three and three respectively).

Jagasia et al 2020 reported two fatal TEAEs in patients treated with ruxolitinib (pulmonary haemorrhage, sepsis). Both were considered related to both ruxolitinib and corticosteroid treatment.

Cytopaenia

Zeiser et al 2020 reported that up to day 28, common adverse events reported in the ruxolitinib and control groups were thrombocytopaenia (33% vs 18%) and anaemia (30% vs 28%).

Although Jagasia et al 2020 reported that all 71 patients treated with ruxolitinib had at least one TEAE, adverse events deemed to be related to ruxolitinib occurred in 53 patients (74.6%), with the most common being anaemia (35.2%), decreased platelet count (32.4%) and decreased neutrophil count (26.8%).

\(^9\) A grade 3 adverse event is severe, a grade 4 adverse event is life-threatening or disabling
Zeiser et al 2015 reported cytopaenia in 30/54 (55.5%) patients; 18/54 (33.3%) had grade III cytopaenia and 3/54 (7.3%) had grade IV cytopaenia. The authors noted that cytopaenias are a known side effect of ruxolitinib and preceded treatment with ruxolitinib treatment in 28/54 (51.8%) patients with aGvHD.

**Infection**

Zeiser et al 2020 reported that a common adverse event up to day 28 was cytomegalovirus (CMV) infection (ruxolitinib vs control: 26% vs 21%, significance not reported). Up to day 28, infection of grade III severity occurred in 34 patients (22%) who received ruxolitinib and in 28 patients (19%) who received control therapy; the corresponding values at data cut-off were 56 patients (37%) and 42 patients (28%). No statistical analysis was reported.

Jagasia et al 2020 reported infections in 57/71 patients (80.3%); the most frequent were CMV events (19.7%) including CMV infection (12.7%), CMV viraemia, (5.6%), retinitis (1.4%), sepsis (12.7%) and bacteraemia (9.9%).

Zeiser et al 2015 reported CMV reactivation in 18/54 (33.3%) patients with aGvHD treated with ruxolitinib.

**Haemorrhage**

Zeiser et al 2020 reported that at the data cut-off date, 19 patients (12%) who had received ruxolitinib and 11 (7%) who had received control therapy had grade III or higher bleeding (haemorrhage), with serious adverse events being reported in 10 patients (7%) and eight patients (5%) respectively.

**Treatment discontinuation**

Zeiser et al 2020 reported treatment discontinuation in 111/154 patients (72%) in the ruxolitinib group and in 132/155 (85%) in the control group; the most common reason was lack of efficacy (21% and 44% respectively). The median duration of exposure to therapy was 63 days (range 6–396) in the ruxolitinib group and 29 days (range 1 188) in the control group. Up to day 28, adverse events led to treatment discontinuation in 17 patients (11%) who had received ruxolitinib and seven patients (5%) who had received control therapy.

In Jagasia et al 2020, adverse events led to ruxolitinib discontinuation in 23/71 (32.4%) patients.