Phase II study of maraviroc as aGvHD prophylaxis in children and young adults

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Many patients undergoing allogeneic hematopoietic stem cell transplant (allo-HSCT) develop acute graft-*versus*-host disease (aGvHD). The risk of developing this serious complication depends upon multiple factors, including stem cell source, patient age, the choice of conditioning regimen, and the GvHD prophylaxis used.[1] Current standard aGVHD prophylaxis regimens result in aGvHD rates of 30–70% and come with immune suppression and opportunistic infections.[2] Therefore, novel aGvHD prophylaxis therapies to further improve outcomes for patients are needed.

One such novel approach is inhibition of C-C chemokine receptor type 5 (CCR5), a chemokine expressed on the surface of lymphocytes infiltrating the intestinal tract and liver. Previously, in a phase I study, addition of maraviroc (a CCR5 inhibitor) to standard aGvHD prophylactic regimens showed feasibility, safety, and efficacy of maraviroc in children.[3] More recently, Pooja Khandelwal *et al*.[2] published results from the phase II study (NCT02167451) in the journal *Bone Marrow Transplantation*.

Study design

Patients ≥ 2 years of age, undergoing an allo-HSCT and receiving aGvHD prophylaxis consisting of a calcineurin inhibitor combined with either mycophenolate mofetil, methylprednisolone, or methotrexate were eligible for the study. Maraviroc was administered orally twice a day as 150 mg tablets or as a 20 mg/mL solution, at a daily dose of 300 mg/m^2 for 34 days, starting from Day −3 until Day 30 after stem cell infusion.

Maraviroc was discontinued in case of ≥ Grade 3 liver toxicity regardless of etiology and when renal function dropped to creatinine clearance < 40 mL/min.

Patients were monitored for the incidence of aGvHD for 100 days after transplantation.

Additionally, pharmacodynamic analyses of CCR5 inhibition were performed and the concentration of maraviroc was measured using liquid chromatography or mass spectrometry.

Results

- In total, 17 patients were enrolled in the study
- The median age was 13 years. Baseline patient and disease characteristics are presented in **Table 1**

Table 1. Baseline patient and disease characteristics[2]

Characteristics	**N = 17**
Median age (range), years	13 (2–25)

Underlying diagnosis	
Malignancy	7
Primary immune deficiency	3
Bone marrow failure	5
Hemoglobinopathy	2
Conditioning regimen	
Myeloablative	13
Reduced Intensity	4
Donor relationship	
Unrelated	11
Related	6

Stem cell source	
Bone marrow	14
Peripheral blood	3
GvHD prophylaxis in addition to maraviroc	
Calcineurin inhibitor + methotrexate	6
Calcineurin inhibitor + mycophenolate mofetil	5
Calcineurin inhibitor + methylprednisolone	6
GvHD, graft-*versus*-host disease	

Engraftment

- Median neutrophil engraftment was 12 (10–21) days after stem cell infusion (n = 17)
- Median platelet engraftment was 21 (12–40) days after stem cell infusion (n = 12)
- One patient experienced secondary graft failure but had a successful subsequent transplant

Incidence of aGvHD at Day 100

- Two patients developed Grade II acute skin GvHD
- Four patients developed gastrointestinal (GI) GvHD, including two patients Grade II upper GI GvHD and two patients Grade III lower GI GvHD
- No patient developed liver GvHD

Incidence of aGVHD and chronic GvHD between Day 100 and Day 180

- No new cases of aGvHD were recorded
- Three patients developed chronic GvHD, including one mild case and two severe cases

Maraviroc trough levels and pharmacodynamics

- Majority of patients achieved a median maraviroc concentration of > 100 ng/mL by Day 7 and Day 14 after transplantation
- Two patients had trough levels < 100 ng/mL at all measured time points and one patient had trough levels < 100 ng/mL on Days 0, 14, and 21
- At most time points, maraviroc decreased CCR5 internalization, except in patients with maraviroc trough levels < 50 ng/mL on Day 0 (n = 3) and Day 14 (n = 2)

Safety

- Eight patients did not complete the full course of maraviroc
    - Intermittent compliance due to nausea (n = 1)

    - Withdrawal from the study (n = 1)
    - Treatment discontinuation due to hepatotoxicity (n = 5) and sepsis with decline in renal function (n = 1)
- Four patients died by Day 100 after allo-HSCT, with causes of death including
    - liver failure due to autoimmune hepatitis (n = 1)
    - *Candida* sp. sepsis (n = 1)
    - adenoviral encephalitis with multiorgan failure (n = 1)
    - idiopathic pneumonia syndrome with multiorgan failure (n = 1)
- At a median last follow-up of 638 days (48–1169 days) 11 patients were alive
    - One patient died due to multiorgan failure following late onset sinusoidal obstructive syndrome
    - One patient died due to progressive GvHD
- Although several ≥ Grade 3 adverse effects were reported, none were attributed to maraviroc
- Several patients experienced infections
    - Six patients had 11 episodes of bacteremia before Day 100
    - Two patients had a fungal infection
    - Two patients developed adenovirus encephalitis and adenovirus colitis
    - Five patients (29%) had asymptomatic cytomegalovirus (CMV) viremia and one patient had CMV pneumonitis
    - Four patients (23%) had asymptomatic Epstein–Barr virus viremia

- Four patients (23%) had asymptomatic BK viremia and one patient had BK virus-associated hemorrhagic cystitis

Conclusion

The study demonstrated that maraviroc was safe in children undergoing allo-HSCT. However, the evidence for GvHD prevention using the tested regimen is limited due to a small sample size, various conditioning regimens and aGvHD prophylactic agents, as well as a short follow-up of the study.

The authors of the study recommend close monitoring of maraviroc levels and dose adjustments when possible and suggest less stringent rules of drug administration during hepatotoxicity in further studies.

References:

1. Jacobsohn DA, Vogelsang GB. Acute graft versus host disease. *Orphanet J Rare Dis.* 2007;2:35. DOI: 10.1186/1750-1172-2-35

2. Khandelwal P, Fukuda T, Teusink-Cross A, et al. CCR5 inhibitor as novel acute graft versus host disease prophylaxis in children and young adults undergoing allogeneic stem cell transplant: results of the phase II study. *Bone Marrow Transplant.* 2020. DOI: 10.1038/s41409-020-0888-3

3. Khandelwal P, Fukuda T, Mizuno K, et al. A pharmacokinetic and pharmacodynamic study of maraviroc as acute graft-versus-host disease prophylaxis in pediatric allogeneic stem cell transplant recipients with nonmalignant diagnoses. *Biol Blood Marrow Transplant.* 2016;22(10):1829-1835. DOI: 10.1016/j.bbmt.2016.08.001