COVER PAGE FOR CLINICALTRIALS.GOV

Protocol Title: Maraviroc as graft versus host disease prophylaxis in pediatric and adult stem cell transplant recipients

NCT Number: NCT02167451

Document Version Date: 03/23/2018

Title of study: Maraviroc as graft versus host disease prophylaxis in pediatric and adult stem cell transplant recipients.

Principal Investigator: Pooja Khandelwal, MD

Co-Investigators: Stella Davies MBBS, PhD, MRCP
Ashish Kumar, MD, PhD
Sharat Chandra, MD
Rebecca Marsh, MD
Parinda Mehta, MD
Michael Grimley, MD
Michael Jordan, MD
Kasiani Myers, MD
Jacob Bleesing, MD, PhD
Christopher Dandoy, MD
Alexander A. Vinks, PharmD, PhD
Adam Nelson, MBBS
Mary Christa Krupski, DO, MPH

Statistician: Adam Lane, PhD

Pharmacist: Ashley Teusink, PharmD

Abstract-

Acute graft versus host disease (GVHD) is the most significant complication of stem cell transplant (SCT), with high rates of morbidity and mortality. In children with GVHD, activated donor lymphocytes migrate to target organs and cause characteristic end organ damage to skin gut and liver. Small protein molecules called chemokines mediate the process of migration. CCR5, a chemokine receptor employed by the HIV virus to enter CD4 T cells, is also widely implicated in the pathogenesis of visceral GVHD, mediating migration of T-cells to target organs.

Maraviroc is an oral CCR5 antagonist that is currently FDA approved as antiretroviral therapy for HIV in adults. However, it has also been used to reduce visceral GVHD in murine models.

We hypothesize that addition of Maraviroc to our standard GVHD prophylactic regimen will reduce the incidence of acute visceral (gut and liver) GVHD in children at day + 100 after a stem cell transplant without impacting engraftment. Our initial study will investigate Maraviroc pharmacokinetics and pharmacodynamics to establish appropriate dosing for future studies. In the second stage of the study we will investigate efficacy. Patients will receive Maraviroc orally at the dose established in the first step of the study along with standard graft versus host disease prophylaxis from day -3 to day +30 after transplant, and will be observed until day + 100 for incidence of acute GVHD, infectious complications, relapse and overall survival. This study has high relevance as it may alter the rates of GVHD in children and improve overall survival after SCT.

Purpose of the Study

1. To establish the pharmacokinetics and feasibility of oral Maraviroc in children undergoing allogeneic stem cell transplantation (SCT).
2. To evaluate efficacy and adverse events of Maraviroc in prophylaxis of acute GVHD in children and young adults undergoing allogeneic SCT.
3. To describe the impact of Maraviroc on time to engraftment, rate of complications early mortality after transplant, chronic GVHD and relapse-free survival.

Significance of the Study in Relation to Human Health

Acute GVHD is a serious complication of SCT, associated with significant morbidity and mortality[1]. Despite many efforts to reduce the incidence of GVHD, which include improved donor selection, preparative regimens that include serotherapy with ATG or alemtuzumab, and established graft-versus –host disease prophylactic agents, acute GVHD remains a challenging complication. Further strategies to reduce its incidence are needed[2].

GVHD can be prevented or decreased with a variety of pharmacologic agents and non-pharmacologic techniques. Early transplants were done using post-transplant methotrexate to prevent GVHD; in the 1980s cyclosporine was demonstrated to be superior to methotrexate and in 1986 the combined use of cyclosporine and methotrexate was shown to be superior to single agent prophylaxis[3]. Subsequently, the immunophillin inhibitor tacrolimus was introduced as an alternative to cyclosporine[4]. Large phase III studies comparing tacrolimus and methotrexate (Tac/MTX) with cyclosporine and methotrexate (CSA/MTX) have been performed and failed to demonstrate a significant difference between the two approaches[5]. In the matched, related donor setting, 329 patients were randomized to receive either Tac/MTX or CSA/MTX. The incidence of Grade II-IV acute GVHD was 31.9% in the Tac/MTX arm and 44.4% in the CSA/MTX arm. Similarly, in the unrelated donor study, the incidence of Grade II-IV acute GVHD was 56% among the 46 patients randomized to Tac/MTX and was 74% among the 63 patients randomized to receive CSA/MTX[6]. Based on these data, both CSA/MTX and Tac/MTX can be considered standard prophylactic therapy after SCT. In small children, methotrexate might be replaced with steroids or mycophenolate mofetil to reduce severity of mucositis. Rates of GVHD continue to be high despite these “best available” prophylactic agents. In addition, current GVHD prophylactic therapy function by reducing donor T cell function, impairing immunologic recovery and perhaps limiting the graft versus tumor potential of allogeneic SCT[7,8]. GVHD prophylaxis that could prevent target organ recognition and damage, without impairing immune reconstitution or tumor specific immunity, would represent a major advance in transplantation[9].

Background

The interaction of donor T cells with antigen presenting cells is the first step in the induction of acute GVHD[7]. This interaction is regulated positively or negatively by a multitude of cellular receptors, cytokines, and chemokines[7]. Chemokines are a group of small proteins that act together with their cell surface receptors to direct cells to specific locations throughout the body, and function in T cell trafficking[10]. The role of T-cell trafficking in acute GVHD is a crucial element in its pathogenesis[11]. Donor T cells migrate to secondary lymphoid organs where they recognize alloantigens on either donor or recipient antigen presenting cells [12-14]. These cells become activated, exit the lymphoid tissues and traffic to the target organs (liver, skin, spleen and lungs) and proceed to cause organ damage [15,16]. It is now established that trafficking of donor T cells into target GVHD organs is chemokine dependent [17]. There is evidence of overexpression of CCL2–5, CXCL2, CXCL9–11, CCL17 and CCL27 in the liver, spleen, skin and lungs during acute GVHD, and CXCR3 and CCR5 receptor expression has been observed on T cells associated with acute GVHD in the GI tract and liver[18,19].

CCR5 is a chemokine receptor whose natural ligands are macrophage inflammatory protein-1-alpha (MIP-1α = CCL3) and MIP-1β (CCL4) as well as RANTES (CCL5)[10]. CCR5 is expressed on a subset of T-cells with a memory cell phenotype and on macrophages. It is a G-protein coupled receptor with 7 transmembrane domains.

Del32 is a large 32-bp deletion in the coding region of the CCR5 gene, resulting in deletion and frame-shift and a non-functional receptor. This allele is found at moderately high frequency in European-Americans (8%) but absent in Chinese and Yoruba populations. Approximately 1% of the population is homozygous for the deletion. The allele frequency is around 16% in Northern Europe, 6% in Italy and 4% in Greece. In the Baltic region and in Ashkenazi Jews a relatively high allele frequency was found. There is very little evidence that Δ32 carriers are more susceptible to infections; mainly increased susceptibility to infections with Flaviviruses such as West-Nile virus was described. Therefore this mutation in not considered an immune defect[20]. On the other hand, evidence exists for immune privileges that accompany this mutation. Carriers are less prone to develop severe asthma and other atopic disorders and are less likely to suffer severe rheumatoid arthritis or multiple sclerosis[21]. Long-term effect of CCR5 inhibition is unknown, but these data suggest that this will not cause severe susceptibility to infection, in excess of that normally occurring after SCT. Patients with del32 mutation remain healthy and have a normal life span. Importantly, CCR5 is a major co- receptor for HIV entry into host cells[22].

Maraviroc (Selzentry – Pfizer, formerly UK-427, 857) is the first FDA-approved drug in its class of CCR5- inhibitors[23]. Maraviroc is approved for 2nd line treatment of CCR5-

tropic HIV-infected patients and is a specific slowly reversible small molecule antagonist of the CCR5 receptor, preventing HIV-1 entry into cells[23]. Two pivotal phase III trials (MOTIVATE-1 and MOTIVATE-2) have shown that Maraviroc was able to produce a significant decrease in viral load and an increase in CD4 count in HIV patients who failed standard regimens. Doses used were 150 and 300 mg bid.

Maraviroc is a true antagonist of the CCR5 receptor. It creates an allosteric conformational change in the extracellular domain of the receptor and prevents binding of all 3 ligands (CCL3-5). Maraviroc does not cause any calcium influx, meaning that it has no agonist activity and does not cause internalization of the receptor. Pharmacokinetic data derived from studies in normal volunteers suggest that drug absorption is rapid but bioavailability is 23-33% due to a first pass effect in the liver with maximum concentrations achieved 1–4 h after dosing. Absorption is decreased with food but no efficacy data determined any difference in outcome so the drug is offered without food restrictions.

Maraviroc is extensively metabolized through the CYP3A4 pathway. Renal clearance contributes approximately 23% of total clearance. Inducers and suppressors of CYP3A4 such as rifampin, antiretroviral medications and certain azoles affect its concentration in blood. The drug itself is not a significant inhibitor or inducer of any known metabolic pathway.

The recommended dose to HIV patients is determined by concomitant medications and the drug was thoroughly investigated in combination with many inducers and inhibitors of its metabolic pathway. Adult patients on strong inhibitors of CYP3A should take 150mg bid, patients on strong inducers of CYP3A should take 600mg bid and all other patients should take 300mg bid[23]. In an ongoing pediatric trial, doses of Maraviroc have been established based on body surface area and the presence or absence of strong inducers or inhibitors by pharmacokinetic analysis[24].

The drug is available in oral form only.

Previous Work Done in this Area

Phase II trials in adults with Maraviroc monotherapy in the antiretroviral setting have shown maximum reduction in viral load in 11 days. No effects on blood counts, immunoglobulin levels or lymphocyte subset numbers were observed in phase I/II data.

Phase III studies showed significant improvement in achieving undetectable viral loads when used with a background antiviral combination of 1,2 or 3 drugs (43, 53, 61%

compared with 29% on a standard 3-drug regimen). CD4 recovery rate was also significantly better[23].

Phase III data showed mild side effects which included nausea, diarrhea, headache and fatigue and these were not significantly different from placebo. The drug was well tolerated in all trial phases in adults. Liver enzyme and bilirubin elevation occurred in 9.2% as opposed to 6.2% in the placebo groups. This finding as well as reports of hepatotoxicity with a different CCR5 inhibitor triggered a black box warning for hepatotoxicity. Post-marketing surveillance reveals that no significant events were registered so far[23,25].

In phase 1 congenital HIV trial A4001031, of the 78 children enrolled, 13 patients (17%) had 17 treatment-emergent, non-treatment-related serious AEs: infections and infestations (11), gastrointestinal disorders (1), hepatobilliary disorders (1), investigations (1), musculoskeletal and connective tissue disorders (1), psychiatric disorders (1), and skin and subcutaneous tissue disorders (1).

Fourteen subjects (18%) experienced 32 treatment-related AEs (all mild-to-moderate): gastrointestinal disorders (12), nervous system disorders (5), hepatobilliary disorders (4), metabolism and nutrition disorders (3), skin and subcutaneous tissue disorders (3), reproductive system and breast disorders (2), psychiatric disorders (2), and cardiac disorders (1). Enrollment is currently ongoing and thus far, Maraviroc appears to be a well-tolerated drug in children[26].

The role of CCR5 and its ligands in GVHD have been primarily explored in murine models. It has been reported that CCR5+CD8+ T cells mediate hepatic injury in murine GVHD and a blocking antibody to CCR5 reduces the damage[27].

Recently, the functional states of T cells have been characterized by chemokine receptor expression pattern in humans. The expression of CCR5 is very low on naıve T cells, but is highly up regulated on both CD4+ (Th1) T cells and activated antigen-specific CD8+ T cells suggesting that the chemokine receptor CCR5 is a marker for effector T cells[14,15].

Palmer *et al* investigated the role of CCR5 in skin GVHD and demonstrated that CCR5 expression was present on both CD4+ and CD8+ T cell infiltrates in the skin biopsies of human aGVHD. By using an intracellular cytokine assay, it was found that activated CD4+ T cells that produce inflammatory cytokines TNFa, IL-2, or IFN-g, were positive for CCR5. Thus CCR5 was upregulated upon allostimulation and expressed on activated T cells. In addition, the expression of CCR5 was shown to be restricted only to the proliferating T lymphocytes in this study[27].

Clinical data supporting the role of CCR5 in the allogeneic transplant setting starts with investigation of carriers of the Δ32 mutation in the CCR5 gene. In a meta-analysis of 1227 renal transplant patients, it was shown that homozygous patients had better graft survival, in some cases longer than 20 years[28,29]. It was shown in separate studies that in both acute and chronic renal rejection there is upregulation of the ligands for CCR5.

In the stem-cell transplantation setting, a retrospective study in Poland, where the prevalence of the Δ32 mutation is relatively high, analysis of 186 recipients and 163 donors of stem-cell transplants revealed that recipient Δ32 was a protective factor for acute GVHD of any grade. Δ32 in the donor did not predict outcome but the combination of Δ32 in both donor and recipient was highly protective (0/11 patients had GVHD)

It has been observed in vitro that maraviroc effectively and specifically inhibited CCR5 internalization and reduced RANTES-induced chemotaxis in concentrations achievable in humans, recapitulating a defect observed in homozygotes for the del32-CCR5 polymorphism. Maraviroc had no effect on hematopoietic cell colony formation, T-cell mediated cytotoxicity or T-cell proliferation.

Prevention of GVHD by targeting CCR5 was explored by Reshef et al, who hypothesized that CCR5 inhibition early after allogeneic SCT would reduce lymphocyte chemotaxis and result in low rates of acute GVHD without impairing engraftment or antitumor activity. Thirty eight patients with a median age of 62 years (range 21-74) received a reduced intensity stem cell transplant with fludarabine and busulfan as a preparative regimen, followed by peripheral blood stem cells for a variety of indications (AML, MDS, NHL, myelofibrosis, aplastic anemia, multiple myeloma, CLL, Hodgkin's lymphoma, CML). In addition to standard GVHD prophylaxis of tacrolimus and methotrexate, Maraviroc was given from day -2 to +30 after establishing an oral dose of 300 mg twice daily by initial pharmacokinetic analysis on the first 13 patients. The outcome of incidence of GVHD at day+100 and day + 180 was compared to a cohort of well-matched historic controls who had received a reduced intensity conditioning stem cell transplant. A cumulative incidence of grade II-IV GVHD at day +180 was 23.6+/-7.4%, which was significantly lower than the author's institutional GVHD rate of 38.5%. Virtually no liver or gastrointestinal GVHD was observed until day +100 and incidences of visceral GVHD were low at day +180 (Liver 2.9+/-2.9% Gastrointestinal tract 8.5+/-5%). There was no significant difference in recovery of lymphocyte counts, infectious complications, incidence of relapse of primary malignancy, overall survival and relapse free survival in both groups. However, there was a lower incidence of transplant related mortality in the Maraviroc cohort [30,31].

In the phase 1 study, administration of the drug was briefly suspended in 7 of 13 patients because of grade 3 abnormalities on liver function testing (n=2) or grade 3 or 4 mucositis (n=5). Liver-function abnormalities did not recur when the drug was re-started. The adverse event profile was similar to the expected toxicity observed in patients undergoing reduced intensity conditioned SCT without maraviroc. In addition, there were no viral or fungal infections other than asymptomatic reactivation of cytomegalovirus. The incidence of bacterial infections was not higher than the expected rate for a reduced intensity transplant. In conclusion, Maraviroc was generally well tolerated in this study [30,31].

Research Plan

The study continues seamlessly from one stage to the next and therefore does not have "phases" in the conventional sense. The initial part of the study will be a dose finding and feasibility study. The second stage of the study will involve administering the appropriate dose of Maraviroc to children as a prophylactic agent against acute graft versus host disease. Maraviroc will be added to standard GVHD prophylaxis of a calcineurin inhibitor (cyclosporine or tacrolimus), methylprednisolone, mycophenolate mofetil (MMF) or methotrexate. The study plan is described below.

Number of Subjects

We plan to enroll 65 patients over the course of approximately 5 years.

Selection

This study will be conducted at Cincinnati Children's Hospital, in patients 2 years of age-40 years of age who are undergoing allogeneic stem cell transplant.

Eligibility

Inclusion Criteria

1. Ages- 2 years and $\leq$ 40 years. For Phase I, the dose finding part of the study, enrollment will be limited to ages 2-12 years as adult dosing is already available and it is likely that a teenager metabolizes the drug similar to adults.

2. All diagnoses are eligible
3. Stem cell source must be marrow, peripheral blood stem cells or cord blood from an unrelated or related donor
4. All conditioning regimens are eligible.
5. Patient must be planned to receive a calcineurin inhibitor (cyclosporine or tacrolimus) together with steroid, methotrexate or mycophenolate mofetil as GVHD prophylaxis.
6. Willingness and ability to provide signed informed consent (including assent, for ages 11-17 years)

Exclusion Criteria

1. Documented anaphylaxis to Maraviroc
2. Ex vivo T depleted grafts
3. Abnormal ALT (>/=--5X ULN) on day -3. (This criterion is to be assessed at study enrollment, but it will be confirmed again prior to the first dose of maraviroc)
4. Individuals who are HIV positive will not be enrolled in the study.

Treatment Plan

Dose and schedule of Maraviroc administration-

Maraviroc administration will start on day -3 and will end on day +30 after stem cell transplant, making the total number of days of drug administration 34 days. Our goal is to have steady state Maraviroc concentrations before stem cell infusion (on day 0) and continuing during the period of engraftment. The day of planned stem cell infusion will be recorded as day zero. If the stem cell infusion is given over 2 days, the first of those 2 days will be considered as day zero. Maraviroc will be administered twice daily orally or via enteral tube. Maraviroc absorption is somewhat reduced with ingestion of a high-fat meal; however, it can be given with or without food.

Dosing of Maraviroc will be based on body surface area, which will be assessed prior to starting maraviroc. This is based on the current congenital HIV trial using Maraviroc. We hypothesize that the optimal dose and exposure (as measured by the area under the concentration-time curve; AUC) for GVHD prophylaxis will likely conform to the optimal dose for the congenital HIV population (Table1). However, we recognize that stem cell transplant patients are more highly catabolic and have significantly more

concomitant medications than HIV patients, so are aware that we may find important PK differences.

BSA (m^2)	Dose of Maraviroc to be administered orally
<0.22	40 mg bid
0.2-0.43	100 mg bid
0.44-0.72	200 mg bid
0.73-1.19	300 mg bid
1.20-1.30	300 mg bid
1.31-1.73	300 mg bid
>1.73	300 mg bid

Table 1. Dosing of Maraviroc based on BSA [32].

Drug interactions with maraviroc occur with strong CYP3A4 inducers and inhibitors so these may not be used during the period of administration of maraviroc.

Enzyme Inducers	Enzyme Inhibitors
Carbamazepine	Amiodarone
Phenobarbital	Clarithromycin/Erythromycin
Phenytoin	Azoles (Keto/ Itra/ Vori/Posaconazole)
Rifampin	Verapamil
Rifabutin	Diltiazem
St. John's Wart	Grapefruit Juice
	Antiretroviral medications

Table 2. List of concomitant medications (CYP3A4 inducers and inhibitors) not allowed at enrollment or during study treatment

Adverse effects of Maraviroc

For a complete list of adverse effects, please see page 18 of protocol [23].

Study design-

For the first part of the study, where full AUC analysis will be performed to verify the dose, we anticipate initially enrolling 12 patients to achieve 12 dose verifications. Any patients who do not achieve a complete PK data profile (i.e. due to suboptimal dose or incomplete course of study drug) will be replaced to achieve 12 dose verifications. The total number of patients will still remain 65 (Phase I and Phase II). The age of enrollment for these patients will be limited to 2-12 years old. This age restriction has been imposed because adult dosing for maraviroc in the stem cell transplant setting has already been established and it is likely that teenagers metabolize the drug similar to adults. The second part of the study, where full AUC analysis will not be conducted, will enroll the remaining patients between the ages 2-40 years.

We will enroll eligible patients and maraviroc will be administered as per study rules. Area under the concentration-time curve (AUC) determination will be performed on days 0 +/- 3 days and 10 +/- 3 days to account for weekends, national holidays or clinical deterioration not allowing for scheduled blood draws on the specified days. PK analysis will be performed after the first 3 patients. As per our study design graph, this is not an “interim” analysis , but an analysis to verify PK target attainment which then will drive either further observation or dose escalation. See Figure 1.

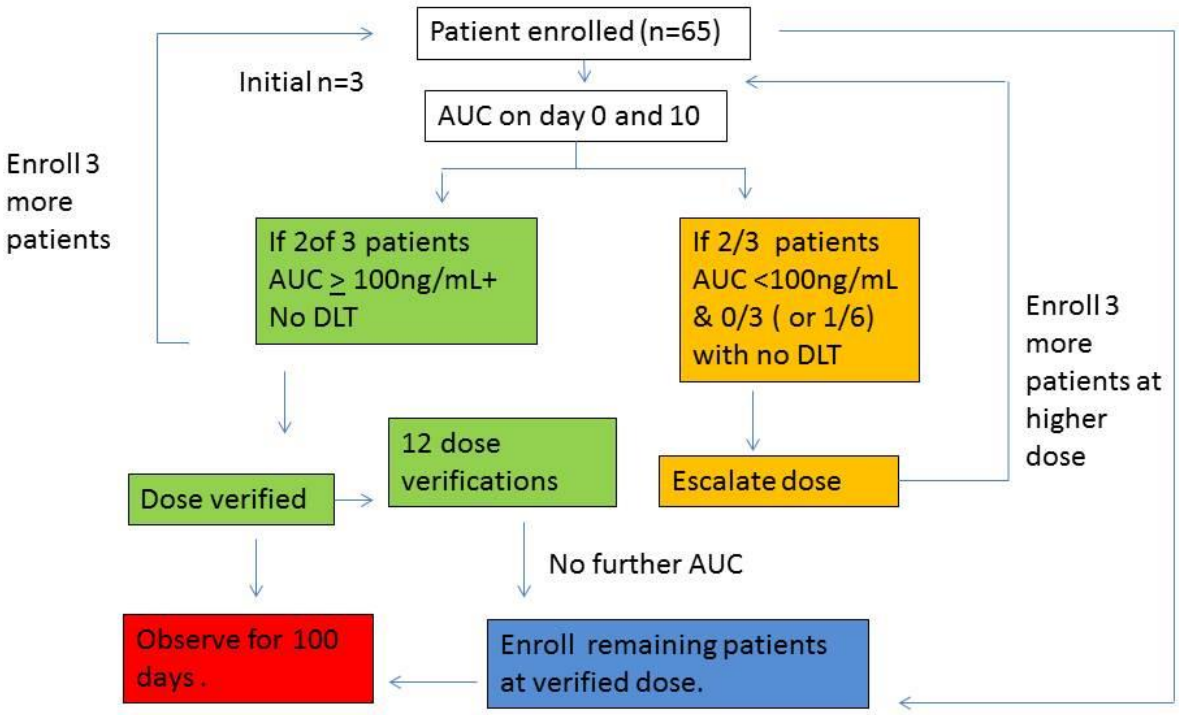

Figure 1. Study design

Pharmacokinetic measurement and analysis-

Blood for PK will be collected on day 0 +/- 3 days and Day 10 +/- 3 days. Complete PK profile (full AUC) will be performed on these days (see time points below). Evaluation of maraviroc trough levels will also be done routinely on all patients on study on days 0,7,14 and 21 in order to collect additional PK data, verify compliance and allow for additional dose corrections if necessary.

Target AUC/12 hours= >/=100ng/mL (based on HIV data)

PK processing will be performed at University of North Carolina's Clinical Pharmacology and Analytical Chemistry Laboratory using mass spectrometer with HPLC separation.

Plasma Maraviroc concentration data will be analyzed by compartmental and non-compartmental analysis with the help of Dr Alexander Vinks, Director of Pediatric Pharmacology Research Unit (PPRU) at CCHMC, and parameter estimates generated will include clearance, half-lives, and volume of distribution along with area under the curve (AUC).

While data on Maraviroc blood levels are available from other studies, our patients are different from those previously studied, and these first cases will be of great value in determining the levels of drug we can achieve in this population

The time points of obtaining drug levels will be as follows:

- Hour 0- Pre maraviroc administration
- Hour 1±10 minutes - After maraviroc administration
- Hour 2±10 minutes- After maraviroc administration
- Hour 4 ±10 minutes- After maraviroc administration
- Hour 6 ± 10 minutes- After Maraviroc administration
- Hour 8 ± 10 minutes- After maraviroc administration
- Hour 12± 20 minutes- After Maraviroc administration

Plasma concentration-time data will be explored graphically and the AUC will be estimated by non-compartmental analysis with the software package WinNonlin (Version 6.2, Pharsight Corporation, Palo Alto, CA). Full maraviroc PK profile and trough concentration data will be analyzed using a PK model-based Bayesian approach (MW/Pharm, MediWare, Groningen, the Netherlands).

Pharmacodynamic analysis will be performed in the laboratory using standard techniques.

Pharmacodynamic assessments will occur on days 0 +/-3 days and one time on day 14 +/- 3 days after stem cell infusion. Results will be available in a timely fashion to correlate with pharmacokinetic test results.

Dose escalation criteria-

Dose escalation will take place if all the requirements listed below are met:

1. The AUC/12 hours of the initial 2/3 patients is below 100 ng/ml

2. No more than 0 of 3 or 1/6 patients on the first dose level experience a dose limiting toxicity by day 30, defined as either-
    a. Non-engraftment by day 30. Engraftment is defined as the first of three consecutive measurements of ANC>500/mcL over 3 or more days.
    b. Grade 4 liver abnormalities, unless clearly related to stem cell transplant and not to the study drug, including but not limited to grade 4-5 liver toxicity due to hepatic veno-occlusive disease, grade 4-5 organ toxicities related to expected infections following stem cell transplant and their sequelae, or grade 4-5 toxicities related to graft versus host disease.
    c. Other grade 4-5 toxicity , unless clearly related to stem cell transplant and not to study drug, including but not limited to veno-occlusive disease of the liver, acute graft versus host disease, autoimmune cytopenias, infectious complications due to stem cell transplant, or organ toxicities due to conditioning regimens.

BSA	Original Dose	Dose escalation	Value increment/dose
<0.22	40 mg bid	50 mg bid	+ 10 mg
0.2-0.43	100 mg bid	120mg bid	+ 20 mg
0.44-0.72	200 mg bid	250 mg bid	+ 50 mg
0.73-1.19	300 mg bid	350 mg bid	+ 50 mg
1.20-1.30	300 mg bid	350 mg bid	+ 50 mg
1.31-1.73	300mg bid	350 mg bid	+ 50 mg
>1.73	300 mg bid	350 mg bid	+ 50 mg

Table 4. Table showing doses and increments for dose escalation of Maraviroc.

Stopping Rules

1. If the incidence of Grade 2-4 acute GI or Liver (visceral) graft versus host disease is greater than 50% in the first 20 subjects by day +100, the study will be stopped. Enrollment will not stop while the analysis is being conducted.

2. If 3 out of 6 subjects experience DLT by day +30 as defined above at the initial dose in the first phase (AUC analysis) of the study, the study will be stopped. Enrollment will not be suspended while the analysis is being conducted.
3. The study will be halted for any grade 4 liver toxicity occurring within 30 days of study drug administration and without clear attributable alternative cause. Enrollment will be suspended while an analysis of the toxicity is being conducted. Enrollment will only restart with approval of the Medical Monitor, IRB and FDA. (Of note: any grade 3 liver toxicity (ALT> 5xULN or Total Bilirubin > 3xULN), regardless of cause, will lead to permanent discontinuation of Maraviroc for that specific patient, but enrollment will continue.)

Primary study end points

1. Feasibility
2. GVHD incidence by day +100 (all grades)
3. pK target >100ng/ml

Secondary Study end points

1. Overall survival by day +100
2. Graft failure by day + 100
3. Primary disease relapse by day +100
4. Incidence of toxicities either due to drug or transplant
5. Infectious complications which include asymptomatic viremias for EBV, Adenovirus, CMV, and/or viral disease, bacterial and fungal infections as documented by blood cultures.
6. Time to neutrophil and platelet engraftment

GVHD will be graded according to IBMTR criteria as shown in table 5 [33]-

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash < 25% BSA	Rash 25-50% BSA	> 50% BSA or generalized erythroderma	Bullae or desquamation
GI	< 500 ml diarrhea	501-1000 ml diarrhea/day	1001-1500 ml diarrhea/day	> 1500 ml diarrhea/day	Abdominal pain and ileus
Liver	Bilirubin < 2 mg/dL	2.1-3 mg/dL	3.1-6 mg/dL	6-15 mg/dL	> 15 mg/dL

Grading		Grade 1	Grade 2	Grade 3	Grade 4
Skin		1	2	3	4
GI		0	1-2	3	4
Liver		0	1-2	3	4

Table 5. Grading and staging of GVHD.

Diagnosis of GVHD is mostly clinical and as such will be on the discretion of the treating physician. Biopsies may aid the diagnosis whenever clinically indicated but are not required in the study.

Clinical Data to be Collected and Reported:

Patients' medical information will be systematically and prospectively collected as is usual for all SCT patients. The data collected will include, but not be limited to-

1. Demographics including age, gender, weight, and height.
2. Underlying diagnosis
3. Specifics of HCT (preparative regimen, type of graft, cell dose, GVH prophylaxis, HLA type and donor relation etc.).
4. Details of engraftment (timing, failure to engraft, loss of graft)
5. Adverse effects directly related to maraviroc and transplant course
6. Onset of GVHD, grade, organ involved and treatments used by day +100
7. Whole blood donor chimerism
8. Infectious complications which include asymptomatic viremias for EBV, Adenovirus, CMV, and viral disease, bacterial and fungal infections as documented by blood cultures or bronchoalveolar lavage cultures/PCRs.
9. Overall survival at day +100
10. Incidence of relapse of primary disease by day +100

Study calendar

All testing below is part of standard evaluation for all patients undergoing allogeneic stem cell transplant and is not dependent on study enrollment, unless marked by "*"

	Enrollment	D-3	D 0 (± 3 days)	D +7 (± 2 days)	D+10 (± 3 days)	D+14 (± 3 days)	D+21 (+ 3 days)	D+30 (+ 7 days)	Monthly after day +30 until day+ 100 (+ 7 days)
Informed Consent*	x								
History and physical examination	x	x	x	x	x	x	x	x	x
GVHD prophylaxis	x	x	x	x	x	x	x	x	x
CYP3A4 enzyme inducers or inhibitors *	x	x	x	x	x	x	x	x	
Acute GVHD evaluation and treatment								x	x
Full AUC analysis (dose verification part)*			X		X				
pK trough*			X	x		x	x		
pD*	X		X			X			
LFTs/CBCD/ Renal profile	x	x	x	x	x	x	x	x	x
Adverse event evaluation*		Continuous							
Compliance*		x	x	x	x	x	x	x	
Chimerism(whole blood)								x	Day + 100
Survival									Day + 100

Study calendar for blood draws for patients undergoing formal AUC analysis-

Days	AUC	Trough drug level	Pharmacodynamic assessment
Pretransplant			x
Day 0	X (±3 days)		X (±3 days)
Day 7		x (±2 days)	
Day 10	X (±3 days)		
Day 14		x (±3 days)	X (±3 days)
Day 21		x (±3 days)	

Table 6. Study calendar for blood draws for patients undergoing formal AUC analysis

For patients enrolled after maraviroc dose has been verified, the schedule for lab draws is shown on Table 7.

Days	Trough drug level	Pharmacodynamic assessment
Pretransplant		x
Day 0	x (±3 days)	X (±3 days)
Day 7	x (±2 days)	
Day 14	x (±3 days)	X (±3 days)
Day 21	x (±3 days)	

Table 7- Study calendar for blood draws for patients on second phase of study (after PK study complete and dose verified)

Volume of Blood Draws-

For pharmacokinetic analysis, we will need approximately 3 ml of blood, to be collected in an EDTA tube. Real time data results will be available to allow for dosing changes to

be made after the first 3 patients. For pharmacodynamics analysis, we will need 2 ml blood in a sodium heparin tube.

Discontinuation of therapy-

Since most patients experience severe toxicities while undergoing an allogeneic SCT, it will be the investigator's responsibility to determine whether certain adverse events are related to the study drug or not based on previous studies using the agent and the current labeling. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used to report toxicities.

The following events will mandate stopping Maraviroc for a specific patient;

- Grade 3 liver toxicity (ALT> 5xULN or Total Bilirubin > 3xULN) regardless of cause

Maraviroc will not be restarted in these cases.

The following events will mandate holding Maraviroc therapy on a specific patient:

1. Grade 3 or higher toxicity (exclusive of liver toxicity, see section above), not attributable to underlying disease.
2. Infection, which requires treatment with a strong CYP450 inducer or inhibitor (predicted to adversely interact with Maraviroc) such as rifampin.
3. Drop in renal function to creatinine clearance <40 ml/min as measured by GFR or cystatin C.

The drug can be restarted at the same dose after full recovery from the AEs. Maraviroc will be discontinued if the AE recurs after re-challenge. Any grade 3 liver toxicity (ALT> 5xULN or Total Bilirubin > 3xULN) regardless of cause will lead to permanent discontinuation of Maraviroc for that patient. The study will be halted for any grade 4 liver toxicity occurring within 30 days of study drug administration without clear attributable alternative cause (see stopping rules for details). Re-challenge is not permissible in the event of Grade 3 or higher liver toxicity (ALT> 5xULN or Total Bilirubin > 3xULN) regardless of cause. Any grade 1 or 2 toxicities related to study drug will not require study drug to be held.

Early termination of study drug-

Treatment will continue unless one of the following criteria applies:

1. A dose limiting toxicity (DLT) occurs. A DLT is defined as either-
   a.) Non-engraftment by day 30, if assessed by the investigator to be related to the study drug. Engraftment is defined as the first of three consecutive measurements of ANC>500/mcL over 3 or more days.
   b.) Grade 4 liver abnormalities, once other causes for liver toxicity have been ruled out.
   c.) Other grade 4-5 toxicity determined by the investigator to be related with high probability to the study drug.
2. Any grade 3 or higher liver toxicity (ALT> 5xULN or Total Bilirubin > 3xULN) regardless of cause:
   a. Any grade 3 liver toxicity (as defined above) will lead to permanent discontinuation of Maraviroc for that patient.
   b. The study will be halted for any grade 4 liver toxicity occurring within 30 days of study drug administration without clear attributable alternative cause. (See stopping rules for specific details.)
3. Patient decides to withdraw from the study due to inability to take the drug.
4. Poor compliance to drug (missing either 6 consecutive doses (3 days) or 12 intermittent doses in the entire administration period (< 80% compliance).

Patients removed from study for unacceptable adverse events will be followed until the adverse event resolves or stabilizes.

Toxicity Monitoring-

Maraviroc is generally well tolerated in children as noted in the phase 1 congenital HIV trial. However, a black box warning for hepatotoxicity exists. Therefore, liver function tests will be monitored on patients while on maraviroc every 48 hours until day+30 (+ 7 days).

General concomitant medication and supportive care guidelines

Maraviroc is not known to significantly affect any metabolic pathway. However, inhibitors and inducers of the cytochrome P450 metabolic pathway affect its drug level. Generally, patients in this trial will receive prophylactic antifungals as directed by their attending physician, which may include either micafungin or ambisome. Other concomitant medications are allowed except for strong inducers or inhibitors of the cytochrome P450, such as voriconazole, phenytoin, carbamazepine and rifampin. (See table 2).

Should there be emesis within 30 minutes of taking maraviroc, the drug should be re – administered. However, any emesis after 30 minutes of taking maraviroc will not require the drug to be readministered.

Risk to unborn fetus-

It is recommended that patients on study utilize appropriate methods of contraception to prevent getting pregnant or fathering a child as the effects of maraviroc on the unborn fetus is unknown. All female patients routinely undergo a pregnancy test as part of pre bone marrow transplant evaluation and only proceed with transplant when it is confirmed that they are not pregnant. Therefore we will not repeat this test prior to starting maraviroc.

Risk associated with blood draws-

This study will require research blood to be drawn as specified time points as shown in the study calendar. This blood will be drawn from a central line whenever possible and will be combined with routine clinical blood draws whenever possible and will not exceed maximum allowed blood volume for that patient per day per standard of care.

Statistical analysis

The primary objectives of this phase I/II clinical trial are to establish a therapeutic dose of Maraviroc and test the 100 day incidence rate of any GVHD in pediatric patients undergoing allogeneic stem cell transplantation against a historical incidence rate.

Phase I will consist of the determination of a therapeutic dose. A dose escalation procedure outlined in the study design will be conducted until a dose which yields 2 of 3 patients with AUC > 100ng/ml and no drug related toxicities.

All patients in phase I treated at the established dose as well as patients treated at a lower dose yet achieve a therapeutic pharmacokinetic level will be included in further analysis. The historical incidence rate of GVHD in pediatric patients undergoing allogeneic stem cell transplantation with GVHD prophylaxis agent of a calcineurin inhibitor+ methylprednisolone is 16% (BMT 2012 data at CCHMC). Assuming the incidence rate for patients treated at the dose established in phase I is 6% then a sample size of evaluable 65 patients provides an 80% power of detecting a difference between this rate and the historical incidence rate. This sample size determination was computed using a two-sided binomial test.

The exact two-sided 95% confidence intervals for the day 100 incidence rate of grade GVHD will be reported. For time-to-event endpoints, e.g., overall survival and time to occurrence of GVHD, we will present Kaplan-Meier curves and corresponding survival p-values will be computed using log-rank tests. Demographic information such as age and race will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as frequencies for categorical parameters, will be presented

Regulatory Issues-

The protocol and informed consent document for this study will be approved in writing by the Institutional Review Board (IRB) prior to any patient being registered on the study.

Changes to the protocol, as well as a change of study staff, must also be approved by the IRB. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to FDA inspection at any time during the study.

Informed consent will be obtained prior to the treatment of participants.

This protocol will be performed under an investigator-initiated IND.

Study Monitoring and Auditing:

Monitoring and auditing procedures will be followed to ensure that the study is conducted, documented, and reported in accordance with the IRB approved protocol, all applicable federal regulations and guidelines, and applicable regulatory requirements of Cincinnati Children's Hospital Medical Center.

Verification of eligibility will be performed and appropriate documentation of informed consent will be documented for all subjects enrolled into the study. The timeliness of Adverse Event and Serious Adverse Event reporting will be monitored to ensure regulatory compliance. All case report forms (CRF) for the first subject enrolled into the study will be monitored for completeness and quality by comparing data in the case report forms to data in the source documents. Thereafter, a minimum of 10% of enrolled subjects' CRFs will be monitored for completeness and quality by comparing data in the case report forms to data in the source documents.

Data Safety Monitoring Plan

A qualified physician not associated with this particular protocol will be chosen as medical monitor for this study. The medical monitor will meet with the PI or designee and review study data/progress a minimum of every 6 months; more often at the discretion of the PI and/or medical monitor.

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, unanticipated serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the review.

At a minimum, the medical monitor should comment on the outcomes of the event or problem, and in the case of unexpected serious adverse event or death, comment on the relationship to participation in the study. Based on the review of these events, the monitor should make a recommendation regarding study continuation. All decisions regarding study continuation, modification, or termination will be reported immediately or

annually, as appropriate, to the IRB, FDA, and other appropriate agencies. Reports for events determined by either the investigator or medical monitor to be possible or definitely related to study participation and reports of events resulting in death should be forwarded in compliance with current IRB policy and applicable federal regulations.

Adverse Event Reporting

Safety and tolerability for the study drug will be assessed according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE published October 6, 2009). The principal investigator or designee will review adverse events closely and assess the event's relationship to study procedures to determine whether the event is unrelated or, unlikely, possibly, probably or definitely related to the study procedures, especially in relation to the underlying disease and baseline lab values for the patient. All adverse events (except as specified below) will be recorded on case report forms and reported in compliance with CCHMC IRB and federal guidelines. All expected and unexpected Grade 3 and higher adverse events occurring during this study up through 30 days following the last dose of maraviroc will be recorded on the case report forms, unless directly attributable to the underlying disease. The principal investigator will review each event and assess its relationship to study events to determine whether the event is unrelated or, unlikely, possibly, probably or definitely related to the study therapy.

Additionally for this study, events as previously identified as resulting from administration of a stem cell transplant will be considered as expected. The transplant regimen is well known to commonly affect systems such as the hematologic, immunologic and gastrointestinal systems. The following are known complications of transplant- disseminated intravascular coagulation, febrile neutropenia, hemolysis, thrombotic thrombocytopenic purpura, adrenal insufficiency, colitis, constipation, diarrhea, enterocolitis, gastrointestinal pain, malabsorption, mucositis, nausea, pancreatitis, vomiting, dyspepsia, fever, pain, cholecystitis, allergic reaction, serum sickness, upper respiratory infection, urinary tract infection, weight gain/loss, acidosis, alkalosis, anorexia, dehydration, glucose intolerance, iron overload, generalized muscle weakness, reversible posterior leukoencephalopathy syndrome, bladder spasms, cystitis, hematuria, urinary frequency, urinary urgency, irregular menstruation, pruritis, hypertension, purpura, and petechiae. For the purposes of the study, the listed events that are < grade 3 will not be considered adverse events.

Hematologic toxicities which are attributable to the underlying hematological disease will not be considered adverse events; however, grade ≥3 neutropenia will be documented and assessed for attribution.

In the event that any of these known complications of transplant or hematologic toxicities are thought to be at least possibly attributable to the study drug, the event will be recorded and subsequently reported to the FDA and IRB according to current reporting requirements.

Adverse reactions must be reported to the principal investigator who is responsible for the reporting to the Cincinnati Children's Hospital Medical Center IRB according to current guidelines. All Adverse Event reporting is to comply with the current CCHMC IRB policy and applicable federal regulations. If any serious adverse events occur, current guidelines will be followed for expedited reporting to the IRB and FDA.

All serious and medically significant adverse events considered related to maraviroc by the investigator will be followed until resolved or considered stable.

Expected events are those that have been previously identified as resulting from administration of the protocol therapy, those that can be contributed to the underlying condition, and/or those associated with transplant. An adverse event is considered unexpected, for reporting purposes only, when either the type of event or the severity of the event is not listed in the drug package insert, consent and/or protocol.

Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy as determined by the PI.

Other research studies

Patients enrolled in this study may be enrolled of any one of the several approved therapeutic and non-therapeutic BMT research studies. There is no foreseen increase in the cumulative risk to the patient enrolled in this study as well as in a therapeutic or non-therapeutic BMT research study.

Risk assessment recommendation

This study will be of more than minimal risk but with potential for direct benefit to participants

Potential Benefits

The direct potential benefit to patients will be reduction in the incidence of acute visceral graft versus host disease.

Potential Risks, Discomforts, Inconveniences and Precautions

There are risks to the patients which include allergic reaction to the drug, hepatotoxicity, gastrointestinal discomfort, need for placement of a nasogastric tube for reliable administration of the drug and possible infectious complications. Safety data for long term use of Maraviroc are not available.

Confidentiality

Any copies of research records will be kept in locked files and any information stored on computer will be password protected. The information from the study may be published; however, subjects will not be identified in such publications. The publication will not contain information about the subjects that would enable someone to determine their identity as a participant without the subject's authorization.

The Institutional Review Board may have access to these records.

The use of clinical information for research purposes and the protection of privacy will be done in compliance with Cincinnati Children's Hospital Medical Center HIPAA requirements.

Period of Time Estimated to Complete Project as Described

Approximately 65 patients will be enrolled on study, which will occur over a time frame of approximately 5 years.

Funding

There is no outside funding for this study. Patients will not be charged for the drug, pharmacokinetic or pharmacodynamic assays.

Payment for Studies

There will be no compensation to patients.

Methods to be used in procuring consent of subjects

Dr. Khandelwal or one of the other Bone Marrow Transplant Physicians who are co-investigators will consult with the patient and/or the parent/legal guardian to explain the procedures, risks and benefits of the study at the patient/parent's level of understanding. Opportunity will be given to consider the study and have questions answered. Information will be given in a written format in the form of a description of the study, which will include a signature space for consent to be given (see attached patient/parent document).

Prior to the initiation of the study, acknowledgement of the receipt of this information and the subject's freely tendered offer to participate will be obtained in writing from each subject in the study. Participation is voluntary, and all subjects/parents/guardians will give informed consent to participate. Assent will be obtained from patients 11-17 years of age. Information will also be given verbally, and all patients and/or parents will have an opportunity to ask questions.

While we do not plan on targeting non-English speaking patients for enrollment on this study, we do periodically have patients who speak Spanish or Arabic. We will not exclude these patients from this study. We will use a short form or fully translated consent (as applicable) according to the process outlined in the Clinical Management and Resource Support Core Standard Operating Procedures (SOP).

Adverse effects of maraviroc reported in HIV populations-

Likely (>10% of patients):

- Central nervous system: Fever (12%)
- Respiratory: Upper respiratory tract infection (20%), cough (13%)

Less Likely (2-10% of patients):

- Cardiovascular: Vascular hypertensive disorder (3%).
- Central nervous system: Dizziness (8%), insomnia (7%), consciousness disturbances (4%), depression (4%), pain (4%).
- Dermatologic: Rash (10%), pruritus (4%), folliculitis (3%), skin neoplasms (benign; 3%), dermatitis (3%).
- Endocrine & metabolic: Lipodystrophy (3%).
- Gastrointestinal: Abdominal pain (8%), appetite disorders (7%), constipation (5%), dyspepsia (3%), stomatitis (3%).
- Genitourinary: Urinary tract/bladder symptoms (3% to 5%), genital warts (2%).
- Hematologic: Neutropenia (grades 3/4: 4%).
- Hepatic: Transaminases increased (grades 3/4: 2% to 5%), bilirubin increased (grades 3/4: 6%).
- Neuromuscular & skeletal: Parasthesia (5%), sensory abnormality (4%), muscle pain (3%), peripheral neuropathy (3%).
- Respiratory: Bronchitis (6%), sinusitis (6%), breathing abnormality (3%), bronchospasm (2%), respiratory tract/sinus disorder (2%).
- Miscellaneous: Herpes infection (7%), sweat gland disturbances (5%), influenza (2%).

Rare but Serious (<2% of patients):

Abdominal neoplasm, acute cardiac failure, anal cancer, angina, basal cell carcinoma, Bowen's disease, C. difficile colitis, cerebrovascular accident, cholangiocarcinoma, cholestatic jaundice, coronary artery disease, coronary artery occlusion, creatine kinase increased, esophageal candidiasis, esophageal carcinoma, hepatic cirrhosis, hepatic failure, hepatotoxicity, liver metastases, lymphoma, MI, myocardial ischemia, myositis, osteonecrosis, pneumonia, rhabdomyolysis, rhinitis, septic shock, squamous cell carcinoma, syncope, tongue neoplasm, viral meningitis

References cited-

1. Weisdorf D. GVHD the nuts and bolts. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program 2007:62-67.

2. Roy J, McGlave PB, Filipovich AH, et al. Acute graft-versus-host disease following unrelated donor marrow transplantation: failure of conventional therapy. Bone marrow transplantation 1992:10(1):77-82.

3. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. The New England journal of medicine 1986:314(12):729-735.

4. Fay JW, Wingard JR, Antin JH, et al. FK506 (Tacrolimus) monotherapy for prevention of graft-versus-host disease after histocompatible sibling allogenic bone marrow transplantation. Blood 1996:87(8):3514-3519.

5. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. Blood 1998:92(7):2303-2314.

6. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood 2000:96(6):2062-2068.

7. Ferrara JL. Pathogenesis of acute graft-versus-host disease: cytokines and cellular effectors. Journal of hematotherapy & stem cell research 2000:9(3):299-306.

8. Paczesny S, Hanauer D, Sun Y, et al. New perspectives on the biology of acute GVHD. Bone marrow transplantation 2010:45(1):1-11.

9. Melve GK, Ersvssr E, Kittang AO, et al. The chemokine system in allogeneic stem-cell transplantation: a possible therapeutic target? Expert review of hematology 2011:4(5):563-576.

10. Balkwill FR. The chemokine system and cancer. The Journal of pathology 2012:226(2):148-157.

11. Moser B, Loetscher P. Lymphocyte traffic control by chemokines. Nature immunology 2001:2(2):123-128.

12. Kunkel EJ, Butcher EC. Chemokines and the tissue-specific migration of lymphocytes. Immunity 2002:16(1):1-4.

13. Serody JS, Burkett SE, Panoskaltsis-Mortari A, et al. T-lymphocyte production of macrophage inflammatory protein-1alpha is critical to the recruitment of CD8(+) T cells to the liver, lung, and spleen during graft-versus-host disease. Blood 2000:96(9):2973-2980.

14. Wysocki CA, Jiang Q, Panoskaltsis-Mortari A, et al. Critical role for CCR5 in the function of donor CD4+CD25+ regulatory T cells during acute graft-versus-host disease. Blood 2005:106(9):3300-3307.

15. Luther SA, Cyster JG. Chemokines as regulators of T cell differentiation. Nature immunology 2001:2(2):102-107.

16. Sackstein R. A revision of Billingham's tenets: the central role of lymphocyte migration in acute graft-versus-host disease. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2006:12(1 Suppl 1):2-8.

17. Cyster JG. Chemokines, sphingosine-1-phosphate, and cell migration in secondary lymphoid organs. Annual review of immunology 2005:23:127-159.

18. Murai M, Yoneyama H, Harada A, et al. Active participation of CCR5(+)CD8(+) T lymphocytes in the pathogenesis of liver injury in graft-versus-host disease. The Journal of clinical investigation 1999:104(1):49-57.

19. Duffner U, Lu B, Hildebrandt GC, et al. Role of CXCR3-induced donor T-cell migration in acute GVHD. Experimental hematology 2003:31(10):897-902.

20. Martinson JJ, Chapman NH, Rees DC, et al. Global distribution of the CCR5 gene 32-basepair deletion. Nature genetics 1997:16(1):100-103.

21. Prahalad S. Negative association between the chemokine receptor CCR5-Delta32 polymorphism and rheumatoid arthritis: a meta-analysis. Genes and immunity 2006:7(3):264-268.

22. Garzino-Demo A, DeVico AL, Conant KE, et al. The role of chemokines in human immunodeficiency virus infection. Immunological reviews 2000:177:79-87.

23. Carter NJ, Keating GM. Maraviroc. Drugs 2007:67(15):2277-2288; discussion 2289-2290.

24. M Vourvahis LM, B Duncan, T Checcio, C Giaquinto, L Keet, SR Valluri, A Fang, G Mukwaya, J Heera. Update from study A4001031: maraviroc pharmacokinetics in CCR5 tropic HIV-1 infected children aged 2 to <18 years. International Aids Society , Poster MOPE044 2013.

25. Bogunia-Kubik K, Duda D, Suchnicki K, et al. CCR5 deletion mutation and its association with the risk of developing acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Haematologica 2006:91(12):1628-1634.

26. C Giaquinto JF, I Mitha, A Fang, M Vourvahis, LMcfadyen, SR Valluri, C Craig, G Mukwaya, H Valdez, J Heera. Safety and efficacy of maraviroc in CCR5-tropic HIV-1 infected children aged 2 to <18 years. 6th International Aids Society Conference on HIV pathogenesis, treatment and prevention 2011.

27. Palmer LA, Sale GE, Balogun JI, et al. Chemokine receptor CCR5 mediates alloimmune responses in graft-versus-host disease. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2010:16(3):311-319.

28. Fischereder M, Luckow B, Hocher B, et al. CC chemokine receptor 5 and renal-transplant survival. Lancet 2001:357(9270):1758-1761.

29. Ma Q, Gooley TA, Storb RF. CCR5 expression on cells from HLA-matched unrelated marrow donors and graft-versus-host disease. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2010:16(1):132-133.

30. Reshef R. Inhibition of lymphocyte trafficking using a CCR5 antagonist-Final results of a phase I/II Study. ASH abstract 1011 2011.

31. Reshef R, Luger SM, Hexner EO, et al. Blockade of lymphocyte chemotaxis in visceral graft-versus-host disease. The New England journal of medicine 2012:367(2):135-145.

32. Vourvahis M ML, Duncan B, Checchio T, Giaquinto C,Lavoie SR,Valluri SR,Fang A,Mukwaya G, Heera J, Valdez H. Maraviroc pharmacokinetics in CCR5-tropic HIV-1 infected children aged 2-<18 years: preliminary results from study A4001031. 3rd HIV Pediatric Workshop, Rome, Italy 2011:15-16 July 2011.

33. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. British journal of haematology 1997:97(4):855-864.