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REVIEW

Clinical significance of chemokine receptor antagonists

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ABSTRACT

Introduction: Chemokine receptors are important therapeutic targets for the treatment of many human diseases. This study will provide an overview of approved chemokine receptor antagonists and promising candidates in advanced clinical trials.

Areas covered: We will describe clinical aspects of chemokine receptor antagonists regarding their clinical efficacy, mechanisms of action, and re-purposed applications.

Expert opinion: Three chemokine antagonists have been approved: (i) plerixafor is a small-molecule CXCR4 antagonist that mobilizes hematopoietic stem cells; (ii) maraviroc is a small-molecule CCR5 antagonist for anti-HIV treatment; and (iii) mogamulizumab is a monoclonal-antibody CCR4 antagonist for the treatment of mycosis fungoides or Sézary syndrome. Moreover, phase 3 trials are ongoing to evaluate many potent candidates, including CCR5 antagonists (e.g. leronlimab), dual CCR2/CCR5 antagonists (e.g. cenicriviroc), and CXCR4 antagonists (e.g. balixafortide, mavorixafor, motixafortide). The success of chemokine receptor antagonists depends on the selective blockage of disease-relevant chemokine receptors which are indispensable for disease progression. Although clinical translation has been slow, antagonists targeting chemokine receptors with multifaced functions offer the potential to treat a broad spectrum of human diseases.

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1. Introduction

Chemokines are highly conserved cytokines or small signaling proteins secreted by a variety of cell types such as stem cells, B cells, T cells, innate lymphocytes, myeloid cells, dendritic cells, and stromal cells [1]. Chemokines are known for their multifaceted biological functions (e.g. chemotaxis, leukocyte migration, inflammatory) [2–4]. They are important not only for all protective or destructive immune and inflammatory activities but also for the development and homeostasis of the human immune system [1]. Due to its important roles, chemokines are invariably associated with many human diseases such as cancer, viral infections, inflammatory and autoimmune diseases [5–8].

As of today, more than 50 human chemokines have been discovered and they could be classified into four subfamilies (C, CC, CXC, CX3C) based on the relative location of conserved cysteine residues in the N-terminal domain [9]. The activation of chemokine-mediated signaling pathways requires the selective binding of chemokines to chemokine receptors which are expressed on surfaces of target cells. Moreover, seven-transmembrane-spanning chemokine receptors, which are expressed on cell surfaces for chemokine signaling, belong to the family of G-protein coupled receptors. Chemokines from four subfamilies activate more than 20 different human chemokine receptors, forming a complex network of chemokine receptor-ligand interactions [1]. Since a chemokine can bind to multiple chemokine receptors and vice versa, the promiscuity or redundancy of the chemokine system is evolutionarily important to maintain its activity and stability [1,2]. Due to their important roles, chemokines and chemokine receptors are therapeutic targets of antagonists intended for the blockade of chemokine receptor-ligand interactions [10].

The journey of chemokine receptor antagonists began in the middle 1990s when the chemokine receptors CCR5 and CXCR4 were found to be co-receptors of HIV-1 viruses [11]. This gave rise to great interest to develop a treatment for HIV because CCR5 and CXCR4 antagonists may prevent HIV viral entry by blocking the binding of HIV gp120 to its co-receptors CCR5 and CXCR4. Maraviroc, supported by Pfizer, was the first CCR5 antagonist approved by the US FDA in 2007, but it could only be used in HIV-infected patients harboring CCR5-tropic virus, but not CXCR4-tropic virus. As described in our previous reviews, plerixafor was initially developed for its anti-HIV activity [12,13]. This CXCR4 antagonist, however, was accidentally found to be a potent anti-cancer drug which was later approved for the mobilization of hematopoietic stem cells [13]. In addition to the success of maraviroc and plerixafor, many chemokine receptors antagonists have been explored to target different types of chemokines and chemokine receptors to treat a variety of human diseases.

To characterize the trend of chemokine receptor antagonists, our paper is organized as follows. First, the procedure of our literature collection is described. Second, three approved drugs (plerixafor, maraviroc, mogamulizumab) are introduced regarding

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Article highlights

- Plerixafor (Mozobil®) designed for anti-HIV treatment is a potent CXCR4 antagonist that mobilizes hematopoietic stem cells. Under the treatment of plerixafor plus G-CSF, a collection of $\geq 2\times10^6$ CD34 + cells/kg within 4 apheresis days could be achieved in more than 80% of patients with non-Hodgkin's lymphoma or multiple myeloma.
- Maraviroc (Selzentry®, Celsentri®) is a noncompetitive CCR5 antagonist that prevents the binding of HIV envelope glycoprotein to CCR5. In the treatment of HIV-infected patients with CCR5 tropism, the maraviroc-based regimen offers 73% to 78% of virologic response (HIV-1 RNA <50 copies/mL at week 48).
- Mogamulizumab (Poteligeo®) is a defucosylated humanized monoclonal antibody that acts as a CCR4 antagonist. Clinical efficacy of mogamulizumab was approximately 21% and 37% to treat mycosis fungoides and Sézary syndrome, respectively.
- There is an increasing number of experimental chemokine antagonists against almost all chemokine receptors, supporting the potential of chemokine receptor antagonists to treat a broad spectrum of human diseases.

This box summarizes key points contained in the article.

their mechanisms of action, clinical efficacy, re-purposed applications, pharmacokinetics and pharmacodynamics (Table 1). Third, potent chemokine receptor antagonists in ongoing phase 3 trials are briefly highlighted.

2. Data collection

We collected information of chemokine antagonists in completed or ongoing phase 3 trials from ClinicalTrials.gov (www.clinicaltrials.gov) using the terms of 20 chemokine receptors (CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CX3CR1, XCR1, and DARC). Five experimental chemokine antagonists (leronlimab, cenicriviroc, mavorixafor, balixafortide, motixafortide) were identified in the ongoing phase 3 trials. Protein structures of chemokine receptors were retrieved from the RCSB PDB databank (www.rcsb.org).

We collected publications from PubMed using keywords of approved and experimental chemokine receptor antagonists within the publication period from 1999/01/01 to 2019/10/01. To search the most recent studies that were absent in the PubMed, we also searched Google Scholar and journal websites (e.g. NEJM, Lancet, AIDS). In addition, we extracted the drug labeling of three approved drugs (plerixafor, maraviroc, mogamulizumab) from the US FDA database (www.accessdata.fda.gov). Randomized clinical studies at phases 2, 3, and 4 were thereafter collected to summarize clinical efficacy of chemokine receptor antagonists. Therapeutic aspects of chemokine receptor antagonists will be updated on our research platform (www.virusface.com).

3. Plerixafor (Mozobil®)

In our previous reviews [12,13], we described the history of plerixafor (Mozobil®, AMD3100) which acts as a CXCR4 antagonist (Figure 1). This CXCR4 antagonist started with the adventitious impurity JM1657 in a commercial monocyclam preparation intended for evaluating the anti-HIV activity [15]. In a phase 1/2 open-label study, the intravenous infusion of plerixafor (2.5 to 160 μg/kg) showed insufficient antiviral effect against CCR5-tropic HIV-1 and caused severe adverse events such as premature ventricular contractions [16]. Therefore, plerixafor was not pursued for HIV treatment [16]. However, a single parenteral injection of plerixafor surprisingly increased leukocytosis in all healthy volunteers (n = 12) [17]. Subsequent studies revealed that plerixafor could mobilize hematopoietic stem cells from the bone marrow to the peripheral blood in 26 healthy volunteers, leading to consistent and reversible increases of peripheral blood CD34+ cells [18]. Plerixafor could increase the mobilization and collection of CD34+ hematopoietic cells

Table 1. Pharmacokinetic parameters of approved drugs.

	Plerixafor (0.24 mg/kg/day)		Maraviroc	Mogamulizumab
Parameters	Non-Hodgkin's lymphoma	Multiple myeloma	(300 mg BID)	(1 mg/kg)
Plasma protein binding (%)	58 [14]	58 [14]	75.5 [101]	-
C_{max} (ng/mL)	761 [46]	1,029 [46]	618 [102]	21,758* [146]
C_{min} (ng/mL)	-	-	33.6 [102]	-
C_{trough} (ng/mL)	-	-	-	7,544* [146]
$T_{1/2}$ (h)	4.4 [46]	5.6 [46]	22.9 [102]	133* [146]
T_{max} (h)	0.6 [46]	0.5 [46]	3.13 [102]	-
V_d (L)	28.6^M [46]	28.6^M [46]	194 [100]	-
$AUC_{0\text{-}12hr}$ (ng×hours/mL)	-	-	2,550 [102]	-
$AUC_{0\text{-}10hr}$ (ng×hours/mL)	3,034 [46]	3,945 [46]	-	-
$AUC_{0\text{-}7days}$ (ng×hours/mL)	-	-	-	1,879* [146]
$AUC_{0\text{-}last}$ (ng×hours/mL)	3,768 [46]	5,260 [46]	-	-
Central volume of distribution (L)	-	-	-	$3.6^{\#}$
Metabolism by CYP	-	-	3A4; 3A5 [101,105]	-
F (%)	-	-	33 [100]	-
Effect of food	-	-	No effect [102]	-
Urinary excretion (%)	-	-	19.6 [101]	-
Fecal excretion (%)	-	-	76.4 [101]	-

Abbreviations: C_{max}: maximum plasma concentration, C_{min}: minimum plasma concentration, C_{trough}: plasma trough, $T_{1/2}$: elimination half-life, T_{max}: time to maximum plasma concentration, V_d: apparent volume of distribution, AUC: area under the plasma concentration-time curve, F: bioavailability.
M: median value.
*: Data was collected after the first infusion of mogamulizumab.
#: Data was retrieved from the FDA label.

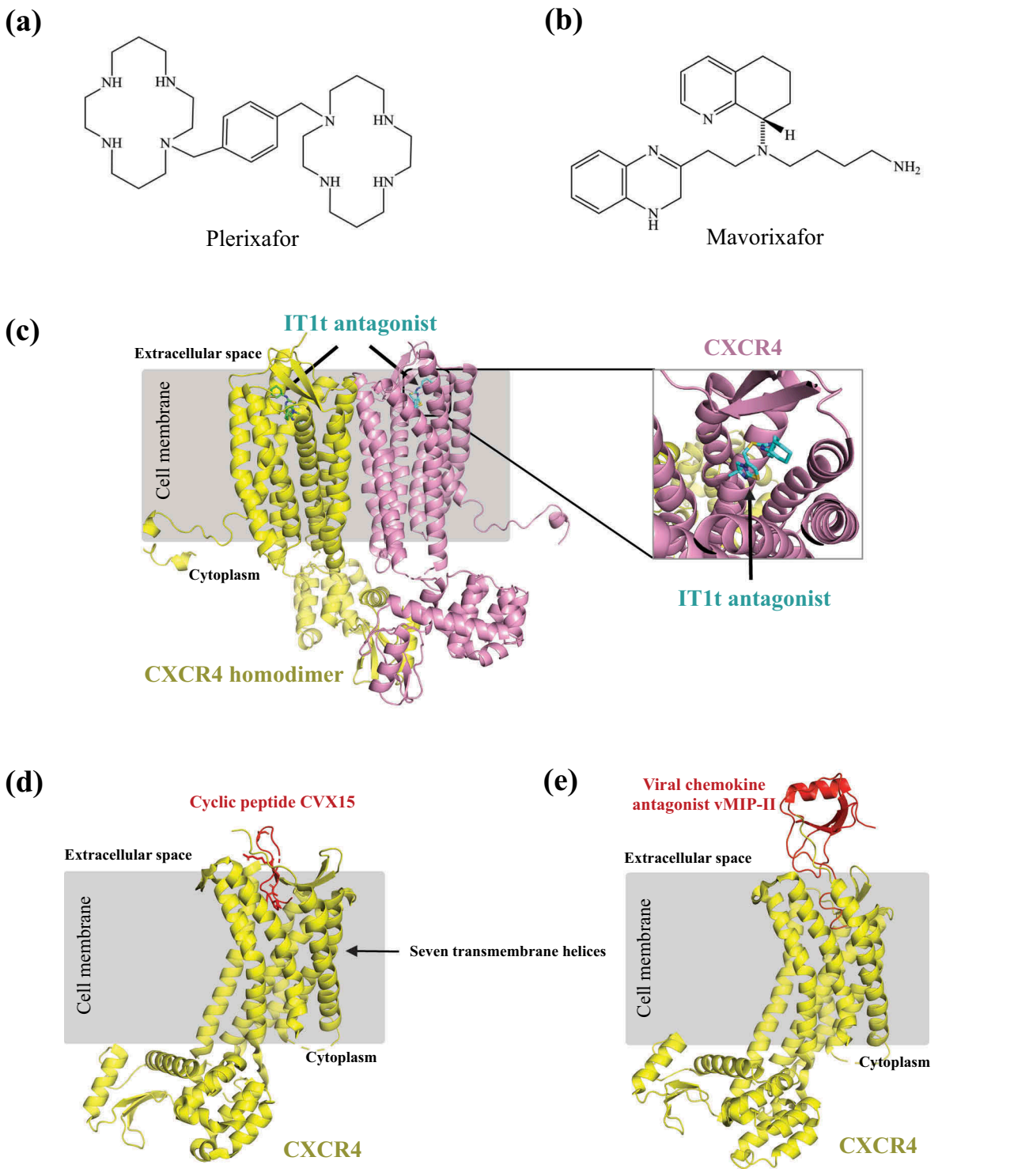

Figure 1. Structures of CXCR4 antagonists and their mechanisms of action.

(a) Chemical structure of plerixafor, an approved CXCR4 antagonist. (b) Chemical structure of mavorixafor, an experimental CXCR4 antagonist. (c) Structure basis of CXCR4 antagonist IT1t that blocks the chemokine binding pocket of CXCR4 (PDB code: 3ODU). Seven transmembrane helices of CXCR4 homodimer are located within the schematic view of the cell membrane. (d) Structure basis of the cyclic peptide CVX15 that blocks the chemokine binding pocket of CXCR4 (PDB code: 3OE0). (e) Structure basis of the viral chemokine antagonist vMIP-II that blocks the chemokine binding pocket of CXCR4 (PDB code: 4RWS). Protein structures are visualized using the PyMOL V1.7 (https://pymol.org).

stimulated by the granulocyte-colony-stimulating factor (G-CSF) [19].

In December 2008, the subcutaneous injection of plerixafor (0.24 mg/kg/day) was approved in combination with G-CSF (10 μg/kg/day) to mobilize hematopoietic stem cells prior to the initiation of apheresis sessions for autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM) (Figure 2(a)). The mobilizing ability of plerixafor alone or in combination with G-CSF was supported in both mouse and human studies [20]. In NHL or MM patients, the combination of plerixafor plus G-CSF increased the likelihood of collecting ≥5 × 10^6 CD34+ cells/kg within 4 apheresis days

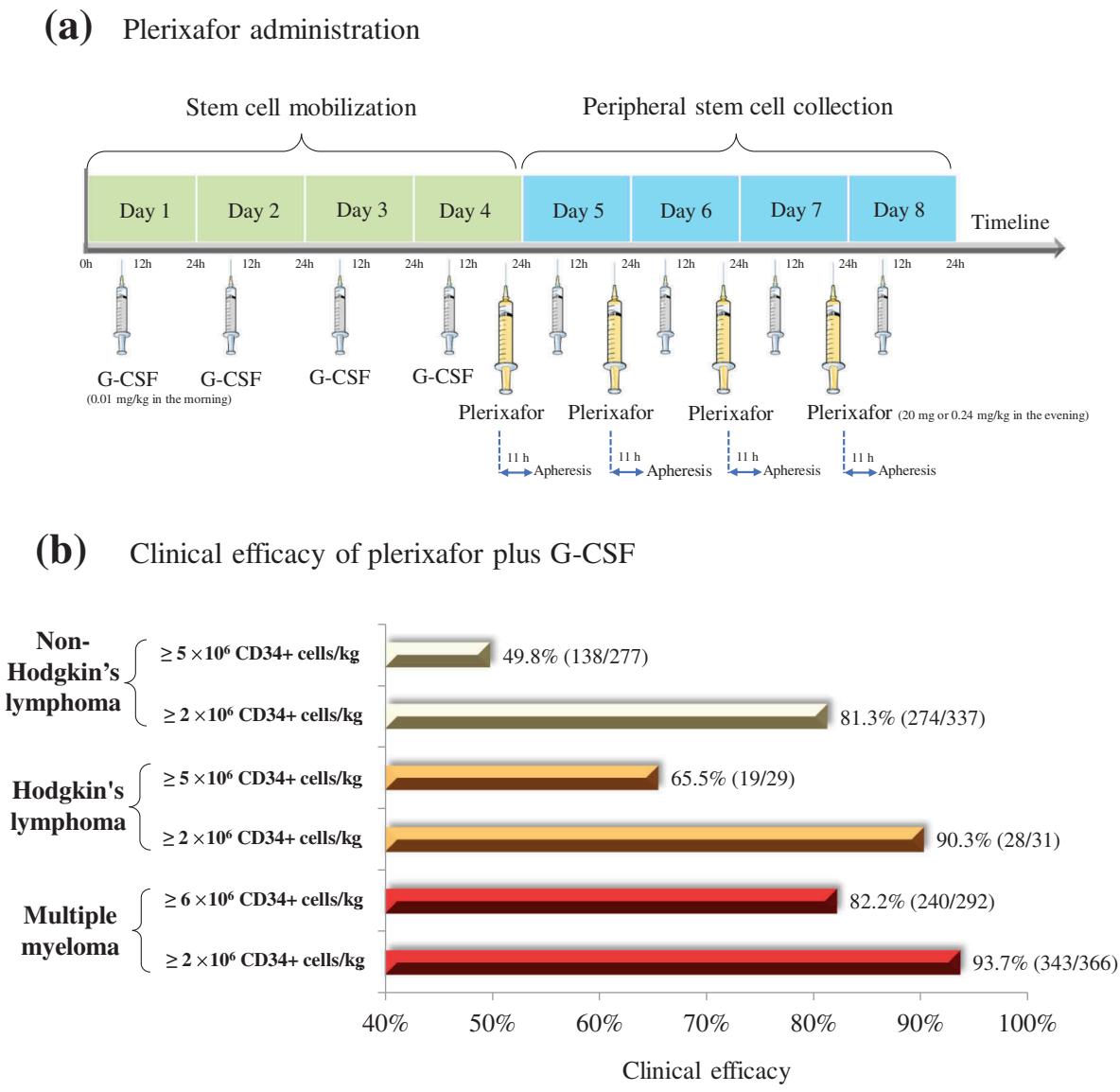

Figure 2. Clinical use of plerixafor plus G-CSF.

(a) Approved administration of plerixafor plus G-CSF. Subcutaneous administration of plerixafor beginning on the evening of day 4 (approximately 11 hours prior to initiation of apheresis). The plerixafor dose is (i) 20 mg fixed-dose or 0.24 mg/kg/day for patients with bodyweight ≤83 kg, or (ii) 0.24 mg/kg/day for patients with bodyweight >83 kg. (b) Clinical efficacy of plerixafor plus G-CSF in clinical trials. Primary outcomes were defined by the proportions of patients achieving $\geq 2 \times 10^6$, $\geq 5 \times 10^6$, or $\geq 6 \times 10^6$ CD34+ cells/kg within 4 apheresis days in the treatment of non-Hodgkin's lymphoma, Hodgkin's lymphoma, and multiple myeloma. Table 2 summarizes the efficacy of plerixafor plus G-CSF and control groups in clinical trials.

compared to G-CSF alone [21]. Notably, autologous stem cell transplantation is a popular procedure to treat many hematological malignancies, but its success depends on the mobilization and collection of hematopoietic stem cells to ensure engraftment. Due to its high cost (around $8,395 per 1.2 mL vial according to https://www.drugs.com), plerixafor is mostly reserved for the patients who fail the mobilization using conventional therapies [22].

3.1. Mechanisms of action

Plerixafor is a CXCR4 inhibitor that reversibly blocks the binding of CXCR4 to its specific chemokine called stromal cell-derived factor-1, also known as CXCL12 [13,33]. The CXCR4-CXCL12 axis leads to changes in actin polymerization, gene expression, cell migration, and cytoskeleton reorganization by activating downstream signaling pathways [34]. The undifferentiated and quiescent state of hematopoietic stem cells is maintained by key factors such as CXCR4 and CXCL12 that protect hematopoietic stem cells from oxidative stress [35]. In addition to its significant role in many physiological and pathological processes [36], the CXCR4-CXCL12 axis plays a key role in the homing and maintenance of hematopoietic stem cells in the microenvironment of stem cell niches within the bone marrow [37].

CXCR4 antagonists such as plerixafor can block the CXCR4-CXCL12 interaction (Figure 1), thereby promoting the migration of hematopoietic stem cells into the peripheral blood [38]. Three acidic anchor-point residues (D171, D262, E288) in CXCR4 are essential for the plerixafor interaction [39]. In fact, plerixafor targets

Table 2. Clinical efficacy of plerixafor – the first approved CXCR4 antagonist.

Study	Subjects	Clinical outcomes	Treatment regimens	Efficacy	Ref.
Study 3101 (phase 3)	Adults with NHL	≥5 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	59.3% (89/150)	[41]
			Placebo+G-CSF	19.6% (29/148)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	86.7% (130/150)	
			Placebo+G-CSF	47.3% (70/148)	
Study 3102 (phase 3)	Adults with MM	≥6 × 10^6 CD34+ cells/kg in ≤ 2 apheresis sessions	Plerixafor+G-CSF	71.6% (106/148)	[42]
			Placebo+G-CSF	34.4% (53/154)	
		≥6 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	75.7% (112/148)	
			Placebo+G-CSF	51.3% (79/154)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	95.3% (141/148)	
			Placebo+G-CSF	88.3% (136/154)	
NCT01767714 (phase 3)	Adults with NHL	≥5 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	62.0% (31/50)	[43]
			0.9% sodium+G-CSF	20.0% (10/50)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	88.0% (44/50)	
			0.9% sodium Chloride+G-CSF	66.0% (33/50)	
NCT00322491 (phase 2)	Adults with NHL	≥5 × 10^6 CD34+ cells/kg in ≤ 5 apheresis sessions	Plerixafor+G-CSF	56.5% (13/23)	[23]
		≥2 × 10^6 CD34+ cells/kg in ≤ 5 apheresis sessions		91.3%(21/23)	
	Adults with MM	≥5 × 10^6 CD34+ cells/kg in ≤ 5 apheresis sessions		96.2% (25/26)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 5 apheresis sessions		100% (26/26)	
–	Adults with NHL	≥2 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions	Plerixafor+G-CSF	58% (28/48)	[24]
		≥5 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions		6% (3/48)	
	Adults with MM	≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions		69% (24/35)	
		≥5 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions		34% (12/35)	
–	Adults with NHL	≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	53% (9/17)	[25]
	Adults with MM			75% (6/8)	
	Adults with HL			100% (2/2)	
NCT 00838357 (phase 3)	Adults with NHL	≥5 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions	Plerixafor+G-CSF	48% (12/25)	[26]
		≥2 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions		80% (20/25)	
	Adults with MM	≥6 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions		89% (80/90)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions		98% (88/90)	
–	Adults with lymphoma	≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	37% (13/35)	[27]
–	Adults with NHL	≥5 × 10^6 CD34+ cells/kg in ≤ 5 apheresis sessions	Plerixafor+G-CSF	74% (32/43)	[28]
		≥2 × 10^6 CD34+ cells/kg in ≤ 2 apheresis sessions		91% (39/43)	
	Adults with HL	≥5 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions		57% (4/7)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 2 apheresis sessions		71% (5/7)	
	Adults with MM	≥6 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions		89% (48/54)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 3 apheresis sessions		98% (53/54)	
NCT00998049 (phase 2)	Adults with MM	≥3 × 10^6 CD34+ cells/kg in ≤ 2 apheresis sessions	Plerixafor+G-CSF	97% (38/39)	[29]
AMD3100-EU21 (phase 2)	Adults with NHL	≥5 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	75% (3/4)	[30]
		≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions		100% (4/4)	
	Adults with MM	≥5 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions		94% (29/31)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions		100% (31/31)	
–	Adults with NHL	≥2 × 10^6 CD34+ cells/kg in ≤ 7 apheresis sessions	Plerixafor+G-CSF	60.3% (38/63)	[31]
	Adults with MM	≥2 × 10^6 CD34+ cells/kg in ≤ 7 apheresis sessions		71.4% (25/35)	
	Adults with HL	≥2 × 10^6 CD34+ cells/kg in ≤ 5 apheresis sessions		76.5% (13/17)	
–	Adults with HL	≥5 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	68% (15/22)	[32]
(phase 2)			G-CSF	15% (15/98)	
		≥2 × 10^6 CD34+ cells/kg in ≤ 4 apheresis sessions	Plerixafor+G-CSF	95% (21/22)	
			G-CSF	78% (76/98)	

Abbreviations: NHL: non-Hodgkin's lymphoma, G-CSF: granulocyte-colony stimulating factor, MM: multiple myeloma, HL: Hodgkin's lymphoma.

the chemokine binding pocket of CXCR4 with a high affinity and displaces the entire N-terminus of CXCL12 to inhibit the CXCR4-mediated signaling [40].

3.2. Clinical efficacy

Clinical efficacy of plerixafor, summarized in Table 2, was supported by three phase 3 trials: the 3101 study in patients with non-Hodgkin's lymphoma [41], the 3102 study in patients with multiple myeloma [42], and a study of 100 randomized Chinese patients with non-Hodgkin's lymphoma [43]. In all these studies, patients received G-CSF (10 μg/kg per day) from day 1 to day 8. Starting on day 5, patients randomly received either plerixafor (0.24 mg/kg/day) or placebo on the evening approximately 11 hours prior to the initiation of apheresis up to four days or the collection of either ≥5 × 10^6 or ≥6 × 10^6 CD34+ cells/kg.

For the treatment of non-Hodgkin's lymphoma, the 3101 study revealed the significant improvement of the primary efficacy (≥5 × 10^6 CD34+ cells/kg within 4 apheresis days) in the group of plerixafor plus G-CSF (59.3%, 89/150) compared to the placebo plus G-CSF (19.6%, 29/148) [41]. In the evaluation of secondary efficacy defined by ≥2 × 10^6 CD34+ cells/kg within 4 apheresis days, the treatment of plerixafor plus G-CSF (86.7%, 130/150) was also superior to placebo plus G-CSF (47.3%, 70/148). Moreover, 90% (135/150) of plerixafor-treated patients underwent transplantation compared to 55.4% (82/142) in the placebo group. In another phase 3 study, the collection of ≥5 × 10^6 CD34+ cells/kg within 4 apheresis days was achieved in 31 (62%) of 50 Chinese patients treated with plerixafor plus G-CSF in comparison to placebo plus G-CSF [43]. In both phase 3 studies, common adverse events were nausea, diarrhea, and injection site reactions.

The 3102 study supported the clinical use of plerixafor in patients with multiple myeloma [42] (Table 2). In the evaluation

of ≥6 × 10^6 CD34+ cells/kg collection within 2 apheresis days, more successes were observed in the group of plerixafor plus G-CSF (71.6%, 106/148) compared to placebo plus G-CSF (34.4%, 53/154) [42]. Furthermore, 148 (95.9%) and 136 (88.3%) patients underwent transplantation in the plerixafor and placebo groups, respectively [42]. In the plerixafor group, common adverse events were gastrointestinal disorders and injection site reactions.

Taken together, the treatment of plerixafor plus G-CSF improves the collection of ≥2 × 10^6 CD34+ cells/kg within 4 apheresis days in more than 80% of patients with non-Hodgkin's lymphoma or multiple myeloma, thereby increasing the success of autologous stem-cell mobilization and transplantation (Figure 2).

3.3. Pharmacokinetics and pharmacodynamics

Plerixafor is an active antagonist of CXCR4 (IC_{50} = 651 ± 37 nM) expressed on the CCRF-CEM T-cells [44]. In healthy volunteers, pharmacokinetic parameters of plerixafor were measured, including absorption rate constant (K_a: 3.6 h^{-1}), peripheral volume of distribution (V_p: 6.93 L), central volume of distribution (V_c: 0.237 L), clearance (5.2 L/h), and intercompartmental clearance (2.31 L/h) [45].

In patients with non-Hodgkin's lymphoma, plerixafor was rapidly absorbed and cleared, while its pharmacokinetic parameters included the maximal observed plasma concentration (C_{max}: 761 ± 101 ng/mL), time to maximal observed plasma concentration (T_{max}: 0.6 ± 0.2 hours), elimination half-life ($T_{1/2}$: 4.4 ± 1.1 hours), and the area under the curve from time 0 to last ($AUC_{0\text{-last}}$: 3768 ± 655 ng×hours/mL) [46] (Table 1). Moreover, the peripheral blood CD34+ count was increased from 16.6 (6.0–83.0) cells/μL at baseline to 52.1 (17.0–182.0) cells/μL after the first dose of plerixafor (0.24 mg/kg/day) [46].

Pharmacokinetic paramaters of plerixafor were also tested in patients with multiple myeloma, including (i) C_{max}: 1029 ± 242 ng/mL [47], (ii) T_{max}: 0.5 ± 0.2 hours, (iii) $T_{1/2}$: 5.6 ± 2.6 hours, and (iv) $AUC_{0\text{-last}}$: 5260 ± 986 ng×hours/mL [46]. After the first dose of plerixafor (0.24 mg/kg/day), the peripheral CD34+ count was increased from 30.0 (6.1–108.3) cells/μL at baseline to 86.9 (45.8–242.0) cells/μL [46].

3.3.1. Dosage

The subcutaneous injection of plerixafor is recommended with a dose of 0.24 mg/kg/day up to 4 consecutive days. After its oral dosing, plerixafor could not be detected in the blood of healthy volunteers [17]. However, plerixafor is rapidly absorbed following subcutaneous injections [17]. The standard dosage of plerixafor is 0.24 mg/kg/day (Figure 2), but should not exceed 40 mg/day according to the FDA label. For patients with moderate and severe renal impairment, its dose should be reduced to 0.16 mg/kg if the creatine clearance is ≤50 mL/min, and this adjusted dosage ensures the safety and efficacy similar to normal patients [48].

3.3.2. Metabolism

Unlike maraviroc, plerixafor is not metabolized by human liver microsomes or primary hepatocytes. Moreover, plerixafor is unlikely to take part in CYP-dependent drug interactions because it does not inhibit or induce cytochrome P450 enzymes [49]. In fact, renal clearance is the primary route of plerixafor excretion. Within the first 24 hours, approximately 70% of a single dose of plerixafor 0.24 mg/kg/day is eliminated by the kidneys in healthy volunteers [49].

3.4. Re-purposed applications

In addition to its use in non-Hodgkin's lymphoma or multiple myeloma, plerixafor can be potentially applied in many human diseases. Here, we summarized five re-purposed applications below.

3.4.1. WHIM syndrome

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare immunodeficiency disease (0.23 cases per million births) caused by amino acid mutations in CXCR4 [13,50,51]. As an effective CXCR4 inhibitor, plerixafor at a low dose could reduce CXCR4 signaling to the normal level rather than a complete blockade [52]. A complete blockade of CXCR4 can cause severe adverse events because CXCR4 is an essential protein that takes part in many physiological processes such as stem cell proliferation, differentiation, and migration [53]. After the twice-daily subcutaneous injection of plerixafor (0.01 to 0.02 mg/kg) for ≥19 months, the wart burden and the frequency of recurrent infections were reduced in three WHIM patients who could not receive G-CSF [54]. In a phase 1 study, the low-dose subcutaneous injection of plerixafor (0.01 to 0.02 mg/kg, twice daily for 6 months) increased circulating leukocytes and corrected panleukopenia in 3 patients with WHIM syndrome [52]. A phase 3 study is ongoing to evaluate the use of low-dose plerixafor versus G-CSF for the treatment of WHIM syndrome (NCT02231879).

3.4.2. Myeloid leukemia

Since leukemia cell trafficking is mediated by CXCR4, CXCR4 antagonists could mobilize leukemia cells from their protective bone marrow niche to treat different types of leukemia (see review [55]). For instance, in patients with chronic myeloid leukemia, plerixafor plus G-CSF could promote the release of leukemic cells from the niche and enhance tumor elimination during the busulfan-fludarabine regimen for allogeneic stem cell transplantation [56]. In a phase 1 study, 69 older adults (56 to 87 years) with acute myeloid leukemia received plerixafor (320 to 810 mcg/kg) and decitabine (20 mg/m^2) which offered the overall response in 30 (43%) patients [57]. In a phase 1/2 study (NCT01141543), 12 patients with acute myelogenous leukemia received the treatment of plerixafor 0.24 mg/kg that increased the absolute neutrophil count ≥0.5 × 10^9/L at the median of 14 days (range: 11 to 18 days) [58]. Plerixafor plus other therapies (e.g. cytarabine, decitabine, etoposide) also induces leukemic blasts into the peripheral blood in children and adults with relapsed/refractory acute leukemia [57,59–61]. Future studies should prove the clinical benefit of plerixafor to treat leukemia based on large-scale cohorts.

3.4.3. Germ cell tumors

Plerixafor was well-tolerated and effective to treat germ cell tumor patients who failed the previous mobilization therapy [62,63]. After the plerixafor-based treatment, 4 of 6 pretreated subjects successfully mobilized a median of 2.6×10^6 CD34+ cells/kg within 6 apheresis days [62]. In a cohort of 21 adults with germ cell tumors, hematopoietic stem cell remobilization with plerixafor plus G-CSF was reported in 17 (81%) patients who collected $\geq 2 \times 10^6$ CD34+ cells/kg within 2 apheresis days [63]. In a retrospective study, 10 patients with relapsed metastatic germ-cell tumors received plerixafor plus G-CSF, while all of them were mobilized with $\geq 4 \times 10^6$ CD34+ cells/kg at the median of 4 apheresis days [64].

3.4.4. Severe β-thalassemia

Plerixafor was safe and acted as an effective agent for rapid mobilization in splenectomized and non-splenectomized patients (N = 10) with severe β-thalassemia [65]. In a phase 1 study (NCT01639690), plerixafor plus G-CSF offered high yields of CD34+ cells and increased β-globin expression in 4 thalassemia patients [66].

3.4.5. Sickle cell disease

Allogeneic hematopoietic stem cell transplantation from matched sibling donors is the only curative treatment for sickle cell patients [67]. In a phase 1/2 study (NCT02242535), a single injection of plerixafor 0.24 mg/kg mobilized $\geq 4.5 \times 10^6$ CD34+ cells/kg in 3 sickle cell patients [68]. Another phase 1 study (NCT02989701) reported a single subcutaneous injection of plerixafor approximately 4 to 6 hours before the apheresis time mobilized 2.9×10^6, 16.4×10^6, and 24.5×10^6 CD34+ cells/kg in 3 sickle cell patients, respectively [69].

4. Maraviroc (selzentry®, celsentri®)

As of September 2019, maraviroc (Selzentry® in the US, Celsentri® elsewhere) is the only CCR5 antagonist approved by the US FDA to treat HIV-1 infections. Maraviroc (UK-427,857) is well-tolerated and can be orally administered in tablets or solution for HIV-1-infected patients with CCR5 tropism, but not CXCR4 tropism. Before the maraviroc administration, testing for CCR5 tropism is recommended each time. Treatment failure of maraviroc (Figure 3(a)) is mostly associated with HIV strains that use CXCR4 for cell entry. The prevalence of CCR5-tropic HIV-1 is approximately 80% in treatment-naive patients, compared to 60% in treatment-experienced patients [70]. Moreover, the tropism prevalence of CCR5, CXCR4, and dual tropism is diverse in different HIV-1 subtypes [71]. Therefore, the co-receptor tropism should be tested using a highly sensitive tropism assay prior to the initiation of maraviroc.

Drug resistance profiles of CCR5 antagonists do not overlap with that of HIV protease inhibitors, reverse transcriptase inhibitors, or integrase inhibitors. For this reason, maraviroc can be beneficially offered for HIV-1-infected patients with drug resistance to other approved antiviral compounds. However, dual therapies containing maraviroc seem to be inferior and should be avoided in first-line treatment [73]. In addition to its approved use against HIV-1, maraviroc is also effective against CCR5-tropic HIV-2 [74]. However, this application is yet to be supported by large-scale clinical trials.

4.1. Mechanism of action

During the viral entry, HIV gp120 binds to the primary receptor CD4 and a co-receptor (e.g. CCR5) in order to fuse viral and host membranes [75]. Chemokine recognition site 2 of CCR5 interacts with the V3 loop of HIV-1 gp120 in viral Env trimer, which is a structural complex formed by gp120 and gp41 [75]. The CCR5-gp120 interaction brings HIV Env trimer closer to host membranes and stabilizes the CD4-induced structure of the HIV Env trimer for viral entry (Figure 3(b)). The inhibition of the CCR5 coreceptor is important for viral prevention. For instance, a small population (approximately 10%) in Europe and western Asia harbor the naturally occurring mutation called CCR5 Δ32, which prevents CCR5 cell surface expression and thus confers resistance to CCR5-tropic HIV-1 infections [76]. Moreover, successful transplantation of hematopoietic stem cells from CCR5 Δ32 donors to one Berlin patient in 2006 and one London patient in 2016 supported the development of HIV-1 remission based on the prevention of CCR5 expression [77,78].

Maraviroc was originally optimized from a high-throughput screening hit called UK-107,453, an imidazopyridine screened for the efficient and potent inhibition of macrophage inflammatory protein-1-beta binding to CCR5 [79]. As a noncompetitive allosteric antagonist, maraviroc targets the chemokine recognition site 2 of CCR5 and stabilizes CCR5 in an inactive conformation, thereby preventing the binding of chemokines and HIV gp120 [80]. Despite the overall similarity between CCR5 and CXCR4, maraviroc cannot efficiently block CXCR4, probably due to the narrow ligand-binding pocket of CXCR4 and the surrounding acidic residues (D97, D171, D187, D193, D262) [80]. Compared to CCR5, the ligand-binding pocket within CXCR4 is more open and these acidic residues are replaced by uncharged residues [80]. Moreover, CCR5 could recognize HIV-1 gp120 variants and many chemokines (e.g. CCL3, CCL4, CCL5, CCL11, CCL14, CCL16), while the binding of CCR5 with its chemokines is mimicked by HIV gp120 [81].

4.2. Clinical efficacy

As summarized in Table 3, clinical efficacy and safety of maraviroc were examined by three phase 3 trials: MOTIVATE-1 (ClinicalTrials.gov Identifier: NCT00098306), MOTIVATE-2 (NCT00098722), and MERIT (NCT00098293). The former two recruited treatment-experienced patients [82], while the latter tested treatment-naive patients [83].

In the pooled analyses of MOTIVATE-1 and MOTIVATE-2 studies, 209 patients in the placebo group received an optimized background therapy (OBT) consisting of three to six anti-HIV drugs, 414 patients received OBT plus 150 mg maraviroc once daily, and 426 patients received OBT plus 150 mg maraviroc twice daily. The rates of virologic responses defined by the HIV-1 RNA <50 copies/mL at week 48 were 17% (35/209), 43% (179/

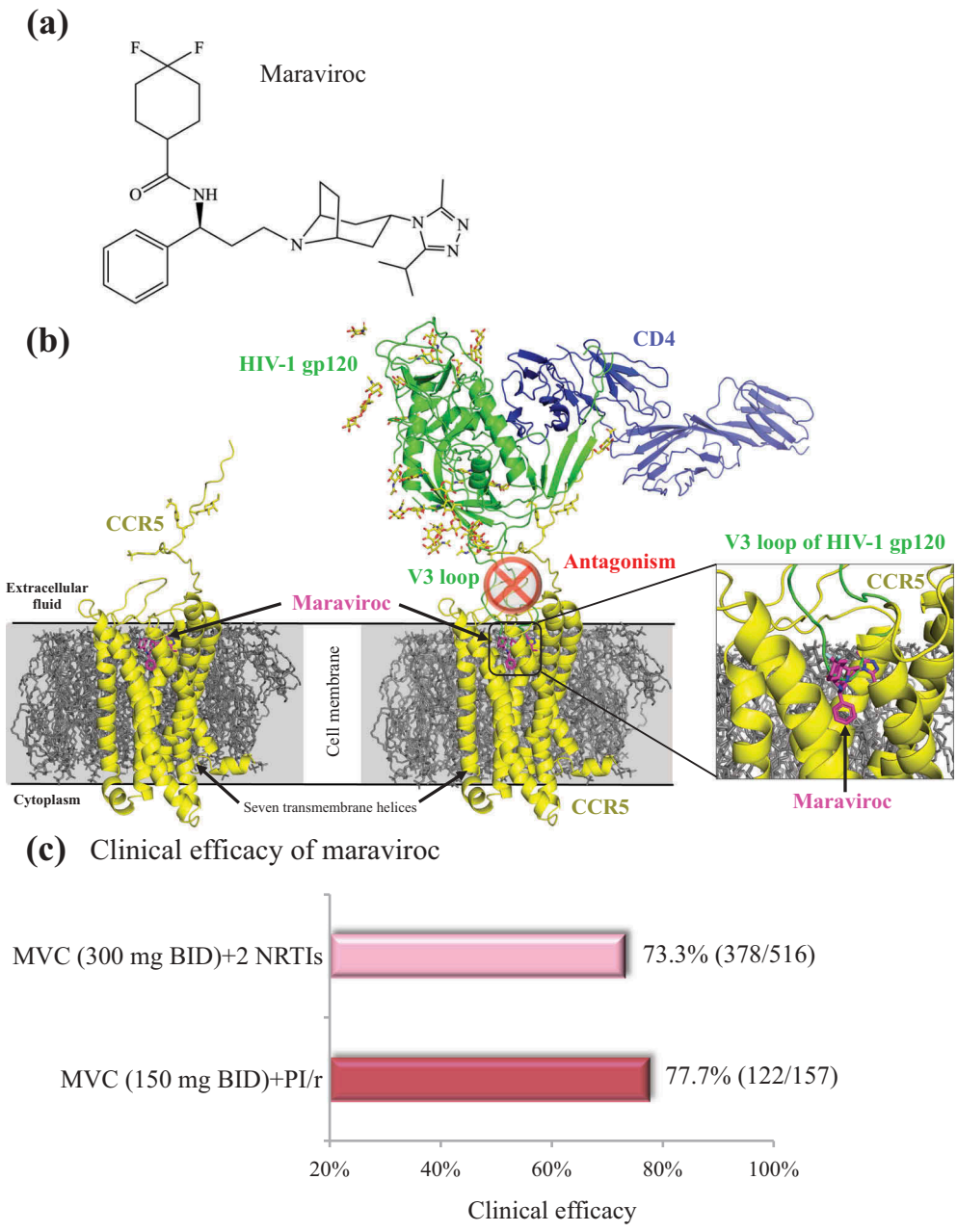

Figure 3. Structural basis and clinical use of maraviroc.

(a) Chemical structure of maraviroc. (b) Structural basis of maraviroc that acts as a CCR5 antagonist to block the binding of HIV-1 gp120 to CCR5 (PDB codes: 6MET, 4MBS). Maraviroc binds to the chemokine binding pocket of CCR5. This binding prevents the interaction between the V3 loop of HIV-1 gp120 and the chemokine binding pocket of CCR5 [75]. (c) Clinical efficacy was defined by the proportions of patients achieving HIV-1 RNA <50 copies/mL at week 48. Table 3 summarizes the efficacy of maraviroc and control groups in clinical trials.

414), and 46% (194/426) in three patient groups, respectively [82]. In a two-year follow-up study, the virologic responses at week 96 were 38.9% (161/414) and 41.3% (176/426) in the once-daily arm and the twice-daily arm, respectively [84]. Under the treatment of maraviroc plus OBT, the virologic response was increased in patients with a low CD4 count and high viral loads at baseline [85]. Regarding the safety profile, maraviroc-treated patients shared similar adverse events with the placebo group [84]. Diarrhea (approximately 10%) was the most common adverse event in the maraviroc arm [82]. A recent study also suggested that the safety and efficacy of maraviroc were similar between adults and pediatric patients [86].

In the MERIT study, maraviroc was a potent inhibitor for treatment-naive patients infected with CCR5-tropic HIV-1 [87,88]. After the 48-week treatment, 235 (65.3%) of 360 patients receiving maraviroc (300 mg twice daily)+zidovudine+ lamivudine achieved the virologic response determined by HIV-1 RNA <50 copies/mL at week 48 [87]. In contrast, the virologic response was observed in 69.3% (250/361) of patients who received efavirenz (600 mg once daily) plus zidovudine and lamivudine [87]. A five-year follow-up study subsequently evaluated HIV RNA <50 copies/mL at week 240 and reported similar virologic responses in the maraviroc arm (50.8%, 158/311) versus the efavirenz arm (45.9%, 139/303) [88]. A significant increase in CD4 counts (293

Table 3. Major clinical trials of maraviroc in the treatment of HIV-1 infections.

Study	Subjects	Clinical outcomes	Treatment regimens	Efficacy	Ref.
MOTIVATE 1 and 2 (phase 3)	Pretreated adults	HIV RNA <50 copies/mL at 48w	MVC (150 mg BID)+OBT	46% (194/426)	[82]
			OBT	17% (35/209)	
		HIV RNA <400 copies/mL at 48w	MVC (150 mg BID)+OBT	56% (239/426)	
			OBT	22% (47/209)	
		HIV RNA <200 copies/mL at 48w	MVC (300 mg BID)+2NRTIs	93.6% (146/156)	[90]
			MVC (150 mg BID)+PI/r	84.1% (132/157)	
			PI/r + 2NRTIs	97.6% (80/82)	
MARCH study (phase 4)	Pretreated adults	HIV RNA <50 copies/mL at 48w	MVC (300 mg BID)+2NRTIs	91.7% (143/156)	
			MVC (150 mg BID)+PI/r	77.7% (122/157)	
			PI/r + 2NRTIs	95.1% (78/82)	
		HIV RNA <200 copies/mL at 96w	MVC (300 mg BID)+2NRTIs	91.7% (143/156)	[91]
			PI/r + 2NRTIs	92.7% (76/82)	
		HIV RNA <50 copies/mL at 96w	MVC (300 mg BID)+2NRTIs	90.4% (141/156)	
			PI/r + 2NRTIs	89.0% (73/82)	
NCT01327547 (phase 4)	Pretreated, co-infected with HCV and/or HBV adults	Grade 3 and Grade 4 ALT abnormalities at 48w	MVC (150, 300 or 600 mg BID)	1.4% (1/70)	[72]
			Placebo	1.5% (1/67)	
		HIV RNA <40 copies/mL at 48w	MVC (150, 300 or 600 mg BID)	80.0% (56/70)	
			Placebo	79.1% (53/67)	
MERIT study (phase 3)	Treatment-naive adults	HIV RNA <50 copies/mL at 48w	MVC (300 mg BID)+2NRTIs	65.3% (235/360)	[87]
			EFV+2NRTIs	69.3% (250/361)	
		HIV RNA <400 copies/mL at 48w	MVC (300 mg BID)+2NRTIs	70.6% (254/360)	
			EFV+2NRTIs	73.1% (264/361)	
		HIV RNA <50 copies/mL at 240w	MVC (300 mg BID)+2NRTIs	50.8% (158/311)	[88]
			EFV+2NRTIs	45.9% (139/303)	
		HIV RNA <400 copies/mL at 240w	MVC (300 mg BID)+2NRTIs	52.4% (163/311)	
			EFV+2NRTIs	46.2% (140/303)	

Abbreviations: HIV: human immunodeficiency virus, w: week, MVC: maraviroc, QD: once daily, BID: twice daily, OBT: optimized background therapy, NRTI: nucleos(t)ide reverse transcriptase inhibitor, PI/r: ritonavir-boosted protease inhibitor, EFV: efavirenz.

cells/μL) was observed in HIV-1-infected patients receiving maraviroc plus zidovudine and lamivudine for 240 weeks [88]. Moreover, a slow recovery of CD4/CD8 ratio driven by less CD8 + T-cell decline was observed in the maraviroc arm [89].

The MARCH study recruited 395 treatment-experienced patients and evaluated whether maraviroc could be used as a switch option for ritonavir-boosted protease inhibitors [90–92]. At week 48, the virologic efficacy was similar between the switched arm of maraviroc+ 2NRTIs and the control arm of one PI/r plus two NRTIs (91.7% versus 95.1%, p-value = 0.32) [90]. A subsequent study evaluated clinical outcomes at week 96 and demonstrated that a maraviroc-based regimen maintained virologic suppression and offered significant reductions of total cholesterol and triglycerides [91]. Both studies supported that the regimen of maraviroc plus two NRTIs offered favorable metabolic changes and good tolerability over 96 weeks, while it could be considered as a switch option of PI/r + 2NRTIs.

In a recent retrospective study, 111 patients were followed up for almost 10 years and the median time of maraviroc-based treatment was 49 months [93]. Of these 111 patients, only 14 (12.6%) patients showed no virological response, while maraviroc was well-tolerated [93]. Taken together, clinical results support that maraviroc is a potent CCR5 antagonist for treatment-naive and treatment-experienced patients infected with CCR5-tropic HIV-1 (Figure 3).

4.3. Drug resistance

A recent study revealed the structural basis of CCR5-gp120 interaction that the V3 loop of HIV-1 gp120 binds to the chemokine-binding pocket of CCR5 [75]. Maraviroc resistance mutations are mostly observed within the V3 loop of gp120, while their prevalence in maraviroc-naive HIV-1-infected patients is rather low (≤5%) [94]. For instance, one to five mutations were observed in the V3 loop of HIV-1 gp120 based on viral sequences from MOTIVATE-1 and MOTIVATE-2 trials [95]. However, these mutations were unique for each patient and no specific signature mutation was reliable to predict maraviroc resistance [95]. Moreover, an alanine insertion between amino acid positions G310 and P311 in the gp120 V3 loop was identified in maraviroc-resistant viruses and this mutation could compensate for the decreased CCR5-binding affinity and improve the viral fusion in cell cultures [96].

Mutations outside the V3 loop of HIV-1 gp120 also contribute to maraviroc resistance. For instance, E172K in the V2 loop (IC_{50}: 1.6 fold change) and/or N302Y in the V3 loop (IC_{50}: 6.0 fold change) reduced drug susceptibility to maraviroc in a T-cell line expressing low levels of CCR5 [97]. HIV-1 chimeric clones bearing a single mutation N425K in the C4 region of gp120 replicated at high concentrations of maraviroc and increased the 40-fold IC_{50} compared to the parental virus [98].

Taken together, the virologic failure of maraviroc is associated with certain amino acid mutations in HIV-1 gp120, but it remains unclear whether signature mutation patterns induce drug resistance to maraviroc [99].

4.4. Pharmacokinetics and pharmacodynamics

As summarized in Table 1, the pharmacokinetics of maraviroc 300mg in healthy subjects were characterized by the mean volume of distribution at steady state (V_{ss}) of approximately 194 liters [100], the absolute bioavailability of 33%, and the

plasma protein binding of 75.5% [101]. In patients infected with asymptomatic CCR5-tropic HIV-1, the minimum (C_{min}) and maximum (C_{max}) plasma concentrations of maraviroc 300mg BID at day 10 were approximately 33.6 and 618 ng/mL, respectively [102]. Furthermore, the time to maximum plasma concentration (T_{max}) and the elimination half-life ($T_{1/2}$) of maraviroc 300mg BID were 3.13 and 22.9 hours, respectively [102]. According to the FDA label, the mean values of the area under the plasma concentration-time curve at hour 12 ($AUC_{0\text{-}12hr}$) were 1865 and 2463 ng×hours/mL in treatment-naive (n = 344) and treatment-experienced (n = 375) patients, respectively. Moreover, no dosing interval adjustments of maraviroc are required in HIV-negative patients with hepatic impairment [103] or renal impairment [104].

4.4.1. Metabolism and dosage

Maraviroc is primarily metabolized by CYP3A5 and CYP3A4 that oxidize and remove small foreign molecules from the human body based on the pathways of oxidation and N-dealkylation reactions [105,106]. Compared to CYP3A4, CYP3A5 has a stronger capacity to metabolize maraviroc into mono-oxygenated metabolites [105]. Moreover, maraviroc unlikely inhibits the drug metabolism mediated by polymorphic CYP enzymes such as CYP2C9, CYP2D6, and CYP2C19 (IC_{50} > 30 μM) [107]. Although unmetabolized maraviroc is the major product excreted after oral dosing, maraviroc is quickly absorbed and extensively metabolized [100].

The concentration of maraviroc is significantly increased by CYP3A inhibitors or reduced by CYP3A inducers such as efavirenz (by approximately 50%). In the absence of potent CYP3A inducers or inhibitors, the standard dose for adults is maraviroc 300 mg twice daily. However, the dosage of maraviroc 300 mg should be adjusted to (i) maraviroc 150 mg in the combination of CYP3A inhibitors such as HIV protease inhibitors (except for tipranavir/r), elvitegravir/r, delavirdine, boceprevir, clarithromycin, itraconazole, ketoconazole, nefazodone, and telithromycin; or (ii) maraviroc 600 mg in the combination of CYP3A inducers (e.g. efavirenz, rifampin, etravirine, carbamazepine, phenytoin, phenobarbital). For pediatric patients (age ≥2 years, bodyweight ≥10 kg), maraviroc dosage is offered based on patient bodyweight, and it is often combined with potent CYP3A inhibitors but not inducers.

The twice-daily maraviroc is an approved standard regimen, but the once-daily maraviroc could be potentially considered in the context of patient adherence and adverse events. In the MOTIVATE-1 and MOTIVATE-2 trials, the virologic response of twice-daily maraviroc was slightly higher than that of once-daily maraviroc (46% versus 43%), but no significant difference was observed (p-value = 0.52) [82]. In a retrospective cohort of treatment-experienced patients, once-daily maraviroc 150mg plus the CYP3A inhibitor darunavir/r offered a promising virologic response of 78% (47/60) at week 48, while this simplified once-daily regimen was well-tolerated with no unexpected adverse event [108]. A recent study proposed the nanoformulation of maraviroc to improve oral absorption and permeability in rat tissues [109]. Furthermore, the long-acting injectable nanoformulation of maraviroc maintained its concentration up to 10 days, supporting its use in HIV treatment and prevention [110].

4.4.2. Distribution and excretion

After single and multiple doses, maraviroc could be distributed in many parts of the human body such as blood plasma, seminal fluid, cervicovaginal fluid, vaginal tissue, and rectal tissues [111,112]. For HIV-negative men, the concentration of maraviroc in rectal tissue was 7.5- to 26-fold higher in rectal tissues than blood plasma, but its saliva concentration was approximately 70% lower compared with maraviroc in blood plasma [112]. For HIV-negative women, a high concentration of maraviroc (>0.5 ng/mL) could be observed in the genital tract within 2 hours [111]. Despite a high concentration of maraviroc in rectal tissues, maraviroc lacks the prophylactic efficacy to prevent simian-HIV infections in macaques [113].

Maraviroc was mainly excreted through feces, while unmetabolized maraviroc was the major component accounting for approximately 42% in human plasma [101]. After a single dose of ^{14}C-labeled maraviroc 300 mg for 168 hours, 76.4% of the radioactivity was obtained in the feces, while 19.6% of metabolic fate was observed in the human urine [101].

4.5. Re-purposed applications

CCR5 is mainly expressed on T lymphocytes, macrophages, and dendritic cells, while its ligands include CCL3, CCL4, and CCL5 [114]. CCR5 is associated with many human diseases such as HIV infections, cerebral malaria, multiple sclerosis, and Rasmussen encephalitis [114]. Due to the multifaced roles of CCR5 in many human diseases [115], maraviroc could be potentially re-purposed for new applications. For instance, the binding of maraviroc to CCR5 significantly increased the transcription (median fold change: 8.1) of unspliced HIV-1 RNA in resting CD4 + T cells through the activation of the NF-κB transcription factor and the subsequent downstream signaling, implying its potential use as a latency reversal agent [116].

4.5.1. HIV pre-exposure prophylaxis

In a phase 2 trial that recruited 406 participants, the dual therapy of maraviroc plus emtricitabine or tenofovir disoproxil fumarate was safe and well-tolerated for HIV pre-exposure prophylaxis in men who have sex with men [117]. In the HPTN 069/ACTG 5305 study, neither maraviroc plus emtricitabine nor maraviroc plus tenofovir disoproxil fumarate increased CD4 + T-cell activation or the CD4+/CCR5+ phenotype, while the maraviroc monotherapy was less effective than combination therapies for HIV pre-exposure prophylaxis in transgender women and men who have sex with men [118]. However, a gel formulation of maraviroc plus dapivirine was active against HIV-1 transmission in the mucosal tissue explants, supporting its use for HIV pre-exposure prophylaxis [119].

4.5.2. HIV post-exposure prophylaxis

The MiPEP trial recruited 213 subjects in England to show that maraviroc 300mg twice daily plus tenofovir disoproxil (200mg)

and emtricitabine (245 mg) once daily offered favorable tolerability and safety for HIV post-exposure prophylaxis [120].

4.5.3. Cancer research

Maraviroc can be used to reduce tumor growth in many cancers (e.g. colorectal cancer). For instance, maraviroc blocks the binding of CCR5 to its ligand CCL5, thereby preventing the monocyte recruitment to the tumor and suppressing the progression of breast phyllodes tumors [121]. Moreover, maraviroc effectively reduced >50% of tumor growth in mice bearing tumor cell xenografts, because CCR5 receptors on classic Hodgkin's lymphoma tumor cells were required for the CCR5-CCL5 signaling in the tumor-microenvironment formation and tumor growth [122]. In patients with colorectal cancer, CCR5 blockade induced the migration of the tumor-promoting microenvironment to achieve favorable clinical responses [123]. Maraviroc efficiently inhibited CCR5 on mesenchymal stem cells, thereby abolishing the colorectal cancer progression [124].

4.5.4. Other applications

CCR5 is a key chemokine receptor in the progression of many human diseases, driving new applications of maraviroc. First, maraviroc could effectively reduce neuropathic pain by decreasing the production of pronociceptive and increasing the production of antinociceptive cytokines [125]. Second, the dual combination of maraviroc plus raltegravir (an integrase inhibitor) could reconstitute the mucosal immunity in the duodenum of treatment-naive patients [126]. Third, maraviroc-based regimen may increase response rates to HBV vaccine in HIV-infected patients [127]. Fourth, maraviroc significantly reduced the risk of arterial stiffness in a small cohort of 6 treatment-experienced male patients who received maraviroc intensification [128]. A subsequent study recruited 21 HIV-suppressed patients at high cardiovascular risk and reported that maraviroc intensification modulated atherosclerotic progression by significant improvements of surrogate noninvasive markers of early atherosclerosis [129]. Fifth, maraviroc is a CCR5 antagonist that reduces astrocytic reactivity and promote motor recovery to treat stroke recovery and traumatic brain injury [130].

5. Mogamulizumab (Poteligeo®)

Mogamulizumab (KW-0761, AMG761) is a defucosylated humanized IgG1 kappa monoclonal antibody. Mogamulizumab (trade name: Poteligeo®) was the first CCR4 antagonist and glycol-engineered antibody approved by the Japanese Ministry of Health to treat adult T-cell leukemia/lymphoma, peripheral T-cell lymphoma, and cutaneous T cell lymphoma [131]. On 8 August 2018, mogamulizumab was approved by the US FDA for the treatment of mycosis fungoides or Sézary syndrome-two major types of cutaneous T cell lymphoma. Notably, the incidence of mycosis fungoides is approximately 5.6 per million persons, while the age-adjusted incidence of Sézary syndrome is 0.1 per million persons [132].

After at least one prior systemic therapy, adults with aggressive/refractory mycosis fungoides and Sézary syndrome could be treated by the weekly intravenous injections of mogamulizumab 1 mg/kg on days 1, 8, 15, and 22 of the first 28-day cycle as well as on days 1 and 15 of subsequent 28-day cycles until disease progression or unacceptable toxicity (Figure 4).

5.1. Mechanism of action

Mogamulizumab is a defucosylated antibody that targets the extracellular N-terminal region of human CCR4, which takes part in the trafficking of lymphocytes to many organs. CCR4 is mainly expressed on Treg and T helper type 2 cells, but it can also be found in memory T-cells, monocytes, platelets, neurons, and endothelial cells [134,135]. CCR4 is a receptor for its major ligands CCL17 and CCL22. This receptor plays an essential role in the recruitment of highly immunosuppressive CD4+, CD25+, and FOXP3+ Treg cells into the tumor microenvironment that is associated with many cancers (e.g. hepatocellular carcinoma) [136,137].

CCR4 is recognized as a therapeutic target for the treatment of T-cell malignancies. CCR4 is overexpressed in patients with T-cell malignancies and its presence is associated with skin involvement and unfavorable clinical outcome [138]. Similar to the defucosylated anti-CCR4 monoclonal antibody KM2760, mogamulizumab may enhance the antibody-dependent cellular cytotoxicity that depletes the target cells [139]. Note that antibody-dependent cellular cytotoxicity is the major mechanism for monoclonal antibodies to act against tumor cells in patients with mycosis fungoides or Sézary syndrome [139].

5.2. Clinical efficacy

Clinical efficacy of mogamulizumab, summarized in Table 4, was mainly evaluated in a phase 1/2 study (NCT00888927) [140], a phase 2, 0761–009 study (NCT01626664) [141], and a phase 3, MAVORIC study (NCT01728805) [142].

In the MAVORIC study, 372 pretreated patients with relapsed/refractory mycosis fungoides or Sézary syndrome were randomly assigned to mogamulizumab (n = 186) or vorinostat (n = 186) [142]. The overall response rate was higher in the mogamulizumab arm (28%, 52/186) than the vorinostat arm (5%, 9/186). In patients with mycosis fungoides and Sézary syndrome, the overall response rate of mogamulizumab arm was 21% (22/105) and 37% (30/81), respectively [142]. A longer period of investigator-assessed median progression-free survival was observed in mogamulizumab-treated patients (7.7 months, 95%CI: 5.7 to 10.3) compared with vorinostat-treated patients (3.1 months, 95%CI, 0.41 to 0.69). In the mogamulizumab arm, the common serious adverse events were pyrexia (4%) and cellulitis (3%) [142].

In the 0761–009 study, 47 pretreated patients with adult T-cell leukemia/lymphoma received the approved dose of mogamulizumab 1.0 mg/kg once weekly for 4 weeks and biweekly thereafter [141]. The overall response rate at week 8 was 11% (5/47) in the mogamulizumab arm compared to 0% (0/24) in the chemotherapy arm [141]. The common treatment-related adverse events were infusion-related reactions, drug eruption, thrombocytopenia, and anemia [141].

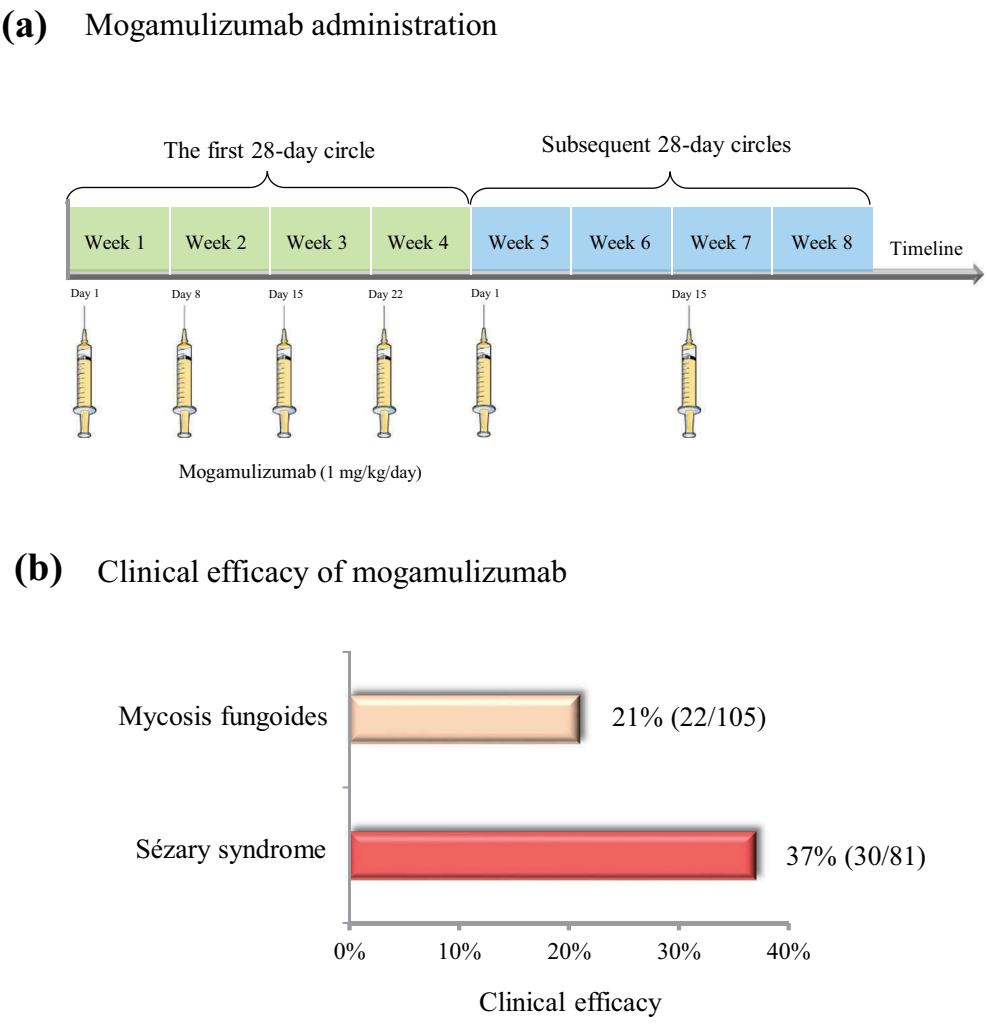

Figure 4. Clinical use of mogamulizumab.

(a) Approved administration of mogamulizumab. Intravenous injections of mogamulizumab over at least 60 minutes are administrated on days 1, 8, 15 and 22 of the first 28-day cycle, then on days 1 and 15 of the subsequent 28-day cycle until disease progression or unacceptable toxicity. (b) Clinical efficacy of mogamulizumab in clinical trials. The clinical efficacy was described by the overall responses, achieved after the treatment of mogamulizumab in mycosis fungoides or Sézary syndrome patients. Table 4 summarizes the efficacy of mogamulizumab and control groups in clinical trials.

Overall, mogamulizumab monotherapy could improve progression-free survival and overall survival rates, with acceptable adverse effects [143]. Treatment of mogamulizumab in patients with receiving hematopoietic stem cell transplantation may induce severe graft-versus-host disease [144].

5.3. Pharmacokinetics and pharmacodynamics

Mogamulizumab could effectively reduce CCR4+ malignant T cells and CCR4+ Treg cells in adults with cutaneous T-cell lymphoma [145]. After the first infusion of mogamulizumab 1 mg/kg, its pharmacokinetic parameters were measured by C_{max} = 21,758 ± 3495.4 ng/mL, C_{trough} = 7544.2 ± 3008.8 ng/mL, $AUC_{0\text{-}7days}$ = 1879.383 ± 464.447 ng×hours/mL, and terminal half-life $T_{1/2}$ = 133 ± 111 hours [146]. After the fourth dose of mogamulizumab 1mg/kg, there was an increase of pharmacokinetic parameters, including C_{max} = 41,373.7 ± 5316.6 ng/mL, C_{trough} = 19,636.7 ± 3825.7 ng/mL, $AUC_{0\text{-}7days}$ = 4224.46 ± 533.16 ng×hours/mL, and $T_{1/2}$ = 438 ± 76 hours [146]. After the eighth infusion, C_{max} = 42.9 ± 14.2 μg/mL, C_{trough} = 33.6 ± 10.6 μg/mL, $AUC_{0\text{-}7days}$ = 6297 ± 1812 ng×hours/mL, and $T_{1/2}$ = 422 ± 147 hours [147]. Furthermore, its clearance time and the central volume of distribution were 12 mL/h (84%), 3.6 L (20%), respectively (Table 1).

5.4. Re-purposed applications

Mogamulizumab could be potentially repurposed to treat other human diseases. (i) In a phase 1/2a study, mogamulizumab reduced 64.9% of HTLV-1 cells by day 15 and decreased levels of inflammatory biomarkers (e.g. CXCL10 decreased 37.3% by day 29) in the cerebrospinal fluid of 21 patients with glucocorticoid-refractory HTLV-1-associated myelopathy-tropical spastic paraparesis [148]. (ii) The reduced expression of FoxP3 + Treg cells was observed in 7 lung and 3 esophageal cancer patients who received the weekly intravenous infusion of mogamulizumab (0.1, 0.5, 1.0 mg/kg) for 8 weeks followed by monthly intravenous infusion until disease progression [149]. During the mogamulizumab treatment, four patients were long survivors with stable disease [149]. (iii) Advanced or metastatic solid tumors using the combination of mogamulizumab and an

Table 4. Clinical efficacy of poteligeo-the first approved CCR4 antagonist.

Study	Subjects	Clinical outcomes	Treatment regimens	Efficacy	Ref.
MAVORIC (phase 3)	Pretreated adults with mycosis fungoides or Sézary syndrome	Progression-free survival (months)	Mogamulizumab Vorinostat	7.7[M] 3.1[M]	[142]
	Pretreated adults with mycosis fungoides	Overall response rate at month 13.1[M] Overall response rate at month 9.1[M]	Mogamulizumab Vorinostat	21% (22/105) 7% (7/99)	
	Pretreated adults with Sézary syndrome	Overall response rate at month 17.3[M] Overall response rate at month 6.9[M]	Mogamulizumab Vorinostat	37% (30/81) 2% (2/87)	
0761-009 study (phase 2)	Pretreated adults with ATLL	Overall response rate at week 8	Mogamulizumab Chemotherapy	11% (5/47) 0% (0/24)	[141]
NCT01173887 (phase 2)	Newly diagnosed patients with ATLL	Overall response rate at week 16	Mogamulizumab+mLSG15 mLSG15	86% (25/29) 75% (18/24)	[151]
NCT00920790 (phase 2)	Pretreated patients with ATLL	Overall response rate at week 8	Mogamulizumab	50% (13/26)	[147]
NCT01192984 (phase 2)	Pretreated patients with PTCL Pretreated patients with CTCL	Overall response rate at week 8	Mogamulizumab	34% (10/29) 38% (3/8)	[133]

Abbreviations: ATLL: adult T-cell leukemia/lymphoma, PTCL: peripheral T-cell lymphoma, CTCL: cutaneous T-cell lymphoma.
M: Median value.

anti-PD-1 antibody called nivolumab [150]. (iv) Newly diagnosed aggressive adult T-cell leukemia-lymphoma using the combination of mogamulizumab and a dose-intensified chemotherapy called mLSG15 [151].

6. Experimental chemokine antagonists

More than 100 experimental chemokine receptor antagonists have been developed to target CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CX3CR1, and XCR1 (see previous reviews [6,152,153]). However, most experimental compounds failed to enter clinical trials, let alone phase 3 trials.

In addition to three approved drugs (plerixafor, maraviroc, mogamulizumab), five promising chemokine receptor antagonists are currently evaluated by phase 3 trials, including: (i) leronlimab, a CCR5 antagonist for HIV treatment; (ii) cenicriviroc, a dual antagonist of CCR2 and CCR5 for treating hepatic fibrosis; (iii) mavorixafor, a CXCR4 antagonist against WHIM syndrome; (iv) balixafortide, a CXCR4 antagonist against metastatic breast cancer; and (v) motixafortide, a CXCR4 antagonist for stem cell mobilization (Table 5). Herein, the recent progress of these candidates is described.

6.1. Leronlimab

Leronlimab (PRO140) is a humanized monoclonal CCR5 antibody that prevents HIV infections by blocking CCR5 on CD4 + cells [154]. In phase 1 and 2 trials with small patient cohorts, leronlimab showed a potent and dose-dependent anti-HIV activity [154]. Of interest, leronlimab could be given subcutaneously once-weekly to achieve potent and durable antiviral activity [155]. For instance, leronlimab 324 mg/weekly decreased 1.51 $\log_{10}$ copies/mL of HIV-1 RNA levels compared with 0.15 $\log_{10}$ copies/mL in the control [154]. The antiviral efficacy and safety profile of leronlimab is summarized by a recent review [156]. The subcutaneous once-weekly injection of leronlimab is currently evaluated in the ongoing phase 2b/3 clinical trial (NCT02859961).

6.2. Cenicriviroc

Cenicriviroc (TBR-652 or TAK-652) is a dual CCR2 and CCR5 antagonist developed for the treatment of HIV and nonalcoholic steatohepatitis [157] (Figure 5). CCR2 is mainly expressed by many cell types such as monocytes, natural killer cells, and T lymphocytes [158]. CCR2 plays an important role in cell trafficking and many pathological diseases such as liver fibrosis, multiple sclerosis, brain tumors, hepatocellular carcinoma, and primary sclerosing cholangitis [158,159].

In an open-label trial, the 24 week once-daily treatment of cenicriviroc improved cognitive performance and reduced monocyte activation in 17 virally suppressed HIV-positive adults with cognitive impairment [161]. In HIV-negative adults with nonalcoholic steatohepatitis, cenicriviroc efficiently improved hepatic inflammation, insulin resistance, and liver

Table 5. Summary of approved and experimental chemokine antagonists.

Target	Antagonist	Type	Indication	Clinical phase
CCR4	Mogamulizumab	Monoclonal antibody	Mycosis fungoides, Sézary syndrome	Approved
CCR5	Maraviroc	Small molecule	HIV-1	Approved
	Leronlimab	Monoclonal antibody	HIV-1	II/III
CCR2/CCR5	Cenicriviroc	Small molecule	HIV-negative hepatic fibrosis	III
CXCR4	Plerixafor	Small molecule	Multiple myeloma, non-Hodgkin's lymphoma*	Approved
			WHIM syndrome	III
	Mavorixafor	Small molecule	WHIM syndrome	III
	Balixafortide	Cyclic peptide	Metastatic breast cancer	III
	Motixafortide	Cyclic peptide	Stem cell mobilization	III

Abbreviations: HIV: human immunodeficiency virus, WHIM syndrome: warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome.
*: Plerixafor plus G-CSF was approved to mobilize hematopoietic stem cells prior to the initiation of apheresis sessions for autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma or multiple myeloma.

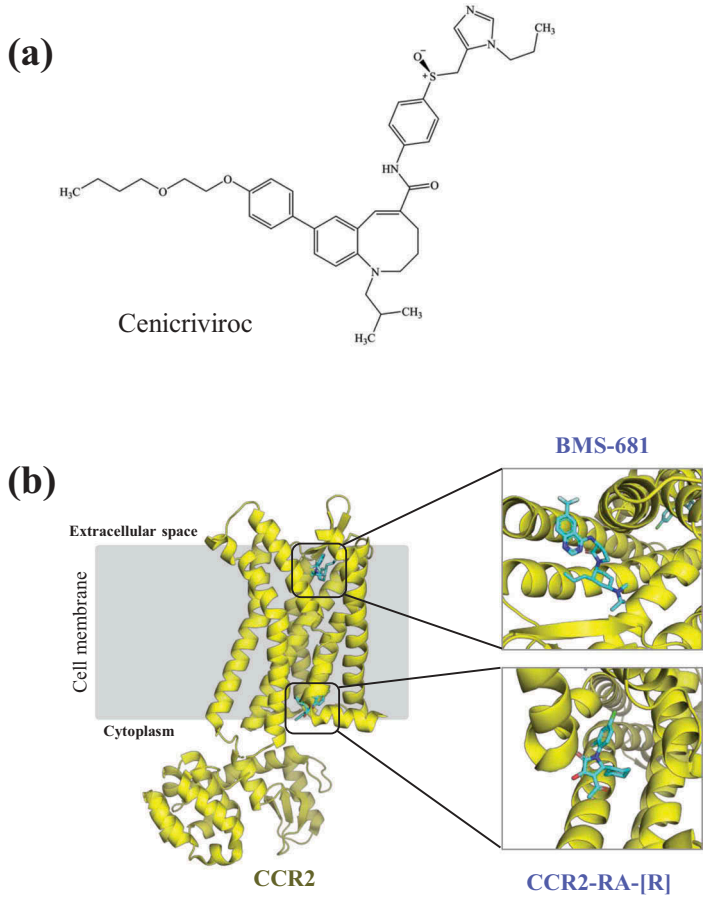

Figure 5. Structural basis of CCR2 antagonists.

(a) Chemical structure of cenicriviroc – a CCR2 antagonist. (b) Structural basis of two CCR2 antagonists that block the ligand-binding pocket of CCR2. BMS-681 and CCR2-RA-[R] act as orthosteric and allosteric CCR2 antagonists, respectively (PDB code: 5T1A) [160].

fibrosis by the inhibition of CCR2+ monocyte recruitment [162]. This was also supported by a recent study that cenicriviroc inhibited the CCL2 signaling and ameliorated alcohol-induced steatohepatitis and liver damage in a mouse model of alcoholic liver diseases [163].

Cenicriviroc is well-tolerated for the treatment of mild or moderate hepatic impairment in HIV-negative adults [164]. In a phase 2b study, the one-year treatment of cenicriviroc 150 mg once-daily significantly improved the fibrosis endpoint in HIV-negative adults with nonalcoholic steatohepatitis and liver fibrosis [165]. An ongoing phase 3 study called AURORA is evaluating cenicriviroc for liver fibrosis in HIV-negative adults with nonalcoholic steatohepatitis (NCT03028740).

6.3. Mavorixafor

Mavorixafor (AMD11070), small-molecule CXCR4 antagonist (IC_{50} = 2.3 ng/ml) that targets a drug-binding pocket of CXCR4 [166] (Figure 1). Mavorixafor exerts a pro-apoptotic effect [167] and inhibits the lung metastasis of oral cancer cells in nude mice [168]. The once-daily oral dosing of mavorixafor (25 or 100 mg) to treat WHIM syndrome is evaluated by phase 2 and 3 trials (NCT03005327, NCT03995108).

6.4. Balixafortide

Balixafortide (POL6326) is a CXCR4 antagonist in the form of cyclic peptide (length: 15 amino acids) that effectively mobilizes hematopoietic stem and progenitor cells in healthy volunteers [169]. The objective response of balixafortide plus eribulin reached 30% (16/54) in the treatment of metastatic breast cancers [170]. The most common adverse events included fatigue (79%, 44/56), neutropenia (57%, 32/56), and infusion-related reactions (48%, 27/56) [170]. Balixafortide versus eribulin is currently evaluated by a phase 3 trial (NCT03786094).

6.5. Motixafortide

Motixafortide (BL-8040, 4F-benzoyl-TN14003) is a 14-amino acid peptide antagonist against CXCR4. This peptide could stimulate the recovery of bone marrow after transplantation [171] and induce the apoptosis of human acute myeloid leukemia blasts [172]. In a phase 1 trial (NCT02073019), the single dose of motixafortide can rapidly mobilize CD34+ cells and immune cells in healthy volunteers [173]. A phase 3 trial (NCT03246529) is currently evaluating the use of motixafortide for stem cell mobilization [174].

7. Conclusion

This review presents a detailed overview of approved and investigational chemokine receptor antagonists that prevent the binding of specific chemokines to their receptors. In the past five years, there is an increasing number of novel chemokine receptor antagonists (n > 100) as well as their clinical trials and publications. Future studies will further our understanding of these chemokine receptor antagonists for clinical use.

8. Expert opinion

8.1. Complexity and multiplicity of the human chemokine system

More than 50 chemokines and 20 chemokine receptors in a variety of human cells have been discovered to form complex interaction networks between chemokines and their receptors. This chemokine system is intricately essential for many inflammatory and autoimmune processes. Human cells can express a variety of chemokines, and some chemokines can bind to several chemokine receptors and vice versa [1,2]. Therefore, the redundancy of chemokines and chemokine receptors remains a therapeutic challenge.

8.2. Identification of disease-relevant chemokine receptors

Many chemokine receptor antagonists failed to show sufficient clinical responses. Why? Treatment failures could be argued on a case-by-case basis, while three reasons could be generalized.

First, human diseases are commonly associated with many chemokine receptors and the blockade of a single chemokine receptor may not be sufficient to block all disease-associated signaling pathways. For instance, CCR1, CCR2, CCR5, and CXCR3 are all involved in the pathophysiology of multiple sclerosis [5]. For this reason, antagonists should target selective chemokine receptors which are highly indispensable for human diseases.

Second, a chemokine receptor often takes part in many immune and inflammatory activities and the blockade of a key chemokine receptor may cause severe adverse events. For instance, CXCR4 inhibition by plerixafor may increase the risk of cardiac dysfunction [12,13]. Aplaviroc, a CCR5 antagonist, was discontinued due to the idiosyncratic hepatotoxicity in a phase 2b trial [175].

Third, due to the redundancy of chemokines and chemokine receptors, an effective dosage of nontoxic, sufficiently metabolically stable antagonists in the circulation is required to block the majority of chemokine receptor-ligand interactions [2]. Moreover, multimerizations of chemokine receptors and the cross-talks between different chemokine receptors further complicate the therapeutic strategies.

8.3. New therapeutic approaches

Recent drug discovery focuses on dual antagonists that target more than one chemokine receptor to overcome species, functional and pharmacological complexity of the chemokine system. Notably, chemokine receptors with seven transmembrane helices share structural similarities in transmembrane binding pockets [9].

As of today, many dual antagonists have been reported: (i) dual CCR2/CCR5 antagonists: cenicriviroc (phase 3, NCT03517540), MK-0812 (discontinued), PF-04634817 (discontinued); (ii) dual CXCR1/CXCR2 antagonists: navarixin (phase 2, NCT03473925), reparixin (phase 2, NCT02370238); (iii) dual CXCR4/CCR5 antagonists: AMD3451, KR21, NF279, PM1-CC [176]; and (iv) dual CCR1/CCR2 antagonists: pyrrolone derivatives [177].

GPCR molecule modeling of small-molecule binding to chemokine receptors offers a promising strategy for virtual screening and drug optimization [9]. As of November 2019, structural data of eight chemokine receptors (CCR2, CCR3, CCR5, CCR7, CCR9, CXCR1, CXCR3, CXCR4) is available in the RCSB protein data bank (https://www.rcsb.org/). Moreover, natural genetic variations of chemokine receptors in human populations are also mapped [178], and the detailed data is available in GPCRdb (https://gpcrdb.org). More than 20 leading compounds were identified in structure-based virtual screening, thereby opening a new era for the development of chemokine receptor antagonists [178].

8.4. Future perspectives

First, proof-of-concept studies of experimental chemokine receptors were mostly conducted using standard cell lines and animal disease models (e.g. mice, rodents). However, these models are not always predictive of complex human diseases [153]. On the one hand, cell-culture models are usually not reliable to model the dynamics of the human immune system, as well as many antagonists and agonists in the circulation. On the other hand, the pathophysiology of human diseases is intrinsically impossible to be modeled by traditional rodent and mouse models due to genomic differences. Future studies should focus on the development of reliable *in vitro* assays and disease models to optimize the pharmacodynamic and pharmacokinetic profiles of chemokine receptor antagonists before the initiation of expensive clinical trials.

Second, combination therapies could be considered for better treatment of human diseases. For instance, the CXCR4 antagonist plerixafor plus a traditional therapy G-CSF was approved for the mobilization of hematopoietic stem cells. Moreover, CXCR4 antagonists and CCR5 antagonists could be combined for the HIV treatment in order to block the entry of HIV viruses with CCR5 and CXCR4 tropisms.

Third, the oral bioavailability of chemokine receptor antagonists is a prerequisite for the potential long-term clinical use with reduced cost compared to monoclonal antibodies or peptides. Moreover, the optimized dose of antagonists that target key disease-associated chemokine receptors is essential for the success of chemokine receptor

antagonists against a broad spectrum of human diseases in the future.

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Declaration of interest

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