CB2R agonists in the clinics: A treasure chest for treating inflammatory diseases

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Researchers give an update on clinical trials with CB_2R agonists and their potential for the treatment of inflammatory diseases

Activation of the type-2 cannabinoid receptor (CB_2R) holds great potential for treating diseases with an inflammatory component. This G-protein-coupled receptor (GPCR) is a key element of the endocannabinoid system (ECS), an important lipid signaling system.

Numerous small molecule activators, so-called CB_2R agonists, demonstrated high efficacy in preclinical disease models for treating a multitude of pathological conditions such as cardiovascular, gastrointestinal, liver, kidney, lung, neurodegenerative/ neuroinflammatory, skin pathologies, rheumatoid arthritis, endometriosis, and eye diseases. (1)

In addition, several of these CB_2R agonists progressed toward clinical stages and might soon provide solutions for high unmet medical needs and inflammatory diseases.

From Cannabis sativa to selective CB_2R agonists

Since at least 1,000 BC, Cannabis sativa has been used for recreational and medicinal purposes, including anti-inflammatory treatments. However, it was not until 1964 that its main active ingredient Δ9-tetrahydrocannabinol (THC) was identified.(2)

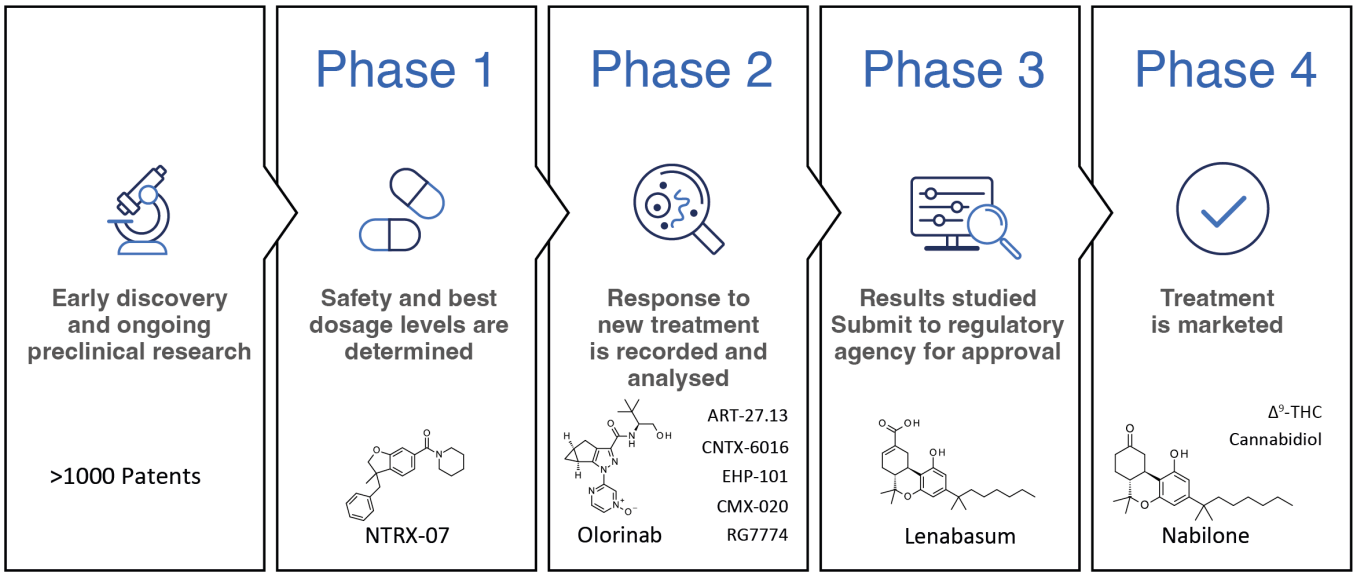
The discovery of its pharmacological targets, the type-1 and type-2 cannabinoid receptors (CB_1R and CB_2R) did not occur until 1988(3) and 1993 (4), respectively. THC is a potent dual CB_1R and CB_2R agonist exhibiting multiple therapeutically relevant physiological properties, including anti-inflammatory, immunosuppressive and analgesic effects. However, central CB_1R-mediated psychotropic upshots resulted in the regulation of its usage.(5)

To overcome this, two drug development strategies were followed by medicinal chemists: i) Limiting drug exposure toward the periphery in order not to engage with brain CB_1R; and ii) enhancing the selectivity over CB_1R.

Clinical trials with CB_2R agonists

Overall, more than 20 CB_2R agonists have been investigated in humans for a wide range of indications. The chemical drug structures in this context are highly diverse.

Fatty acid derivatives, classical and non-classical cannabinoids, and multiple diverse synthetic ligands are included, which also results in the coverage of a broad range of physicochemical properties. (1c, 6)



In clinical trials data on dosage, safety and therapeutic efficacy in humans are generated (Figure 1).

The overall study design aims to ensure the scientific validity and reproducibility of the results. Generally, clinical trials are divided into four phases.[7]

In phase 1 information on the pharmacokinetic profile of a new molecular entity is collected in a small group of people.

Furthermore, safe dose regimens and side effect profiles are determined. Phase 2 concentrates on establishing the preliminary efficacy of the drug in patients, usually against a placebo control group.

Phase 3 aims for final confirmation of the safety and efficacy data and is followed by the launch of the medicine. Finally, phase 4 studies continuously monitor a drug and delineate its risks, benefits, and optimal use over its lifetime.

Launched CB_2R agonists & ongoing clinical trials

The first mostly unselective CB_2R agonists, often bearing unfavourable overall absorption, distribution, metabolism and excretion (ADME) profiles and often focussing on pain indications, were halted in clinics for various reasons but did not raise any CB_2R-related safety concerns.[8]

Phytocannabinoids Dronabinol, which is synthetic THC, Nabilone and Cannabidiol (CBD) exerting their action partially through CB_2R activation, have been introduced to the market. Oral THC is used for treating anorexia, cachexia and chemotherapy-induced emesis.

At the same time, buccal THC has been launched for cancer pain. Nabilone is used for treating patients that suffer from chemotherapy-induced nausea and vomiting. CBD, a non-classical cannabinoid for which the main mode of action is still debatable, is marketed for treating infantile severe myoclonic epilepsy, Dravet and Lennox-Gastaut syndrome, and tuberous sclerosis.

Combinations of CBD and THC have been approved for treating MS-associated spasticity and pain management. Non-psychoactive dual CB_1R/CB_2R agonist Lenabasum is currently being investigated in phase 3 trials for treating systemic sclerosis and dermatomyositis.

The most advanced selective CB_2R agonists are the synthetic cannabinoids Olorinab and RG7774. The clinical focus of Olorinab is on pain related to irritable bowel syndrome (IBS) and IBS with predominant constipation or diarrhoea. RG7774 aims to provide oral treatment to patients suffering from diabetic retinopathy. Arachidonic acid analogue CMX-020 is studied in phase 2 trials to treat pain, osteoarthritis and diabetic neuropathy.

Pain, in particular, neuropathic pain, is also the focus of the selective synthetic CB_2R agonists CNTX-6016 (phase 2) and NTRX-07 (phase 1). Dual CB_1R/CB_2R agonist ART-27.13 is in phase 2, seeking to provide treatment options for cachexia and cancer-related anorexia. Cannabidiol derivative EHP-101, which activates besides CB_2R also PPARγ, is aimed at multiple sclerosis and scleroderma patient populations (phase 2).

Together, these CB_2R agonists hold very high potential for treating multiple diseases in which inflammatory processes play a significant role or are the underlying reasons.

Furthermore, recent advances in expanding the knowledge of CB_2R protein structure and molecular pharmacology will enable the development of the next generation of CB_2R agonist drugs, allowing an even more precise pharmacological targeting, thereby unlocking the high therapeutic potential of CB_2R for treating inflammatory diseases.

Acknowledgements

We thank all colleagues who have contributed to our investigations on CB_2R over the years.

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