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Small molecules with anti-inflammatory properties in clinical development

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ABSTRACT

Inflammation is a crucial physiological response of our body to any kind of noxa be it an infection or tissue injury. However, this physiological process can be detrimental if dysregulated, and when the acute inflammatory response fails to resolve the cause of inflammation, there can be a switch to chronification. According to ICD 10 (WHO) over 3.000 diseases exist with the suffix "–itis" which terms an inflammatory disease. For the treatment of inflammation, non-steroidal anti-inflammatory drugs (NSAIDs) are the most widespread drugs while glucocorticoids are among our strongest weapons against inflammation, making them emergency treatments for acute episodes of chronic inflammation. For the treatment of many inflammatory disorders, both are not satisfying. Consequently, industrial and academic research on anti-inflammatory drugs is very intensive. In this review, we evaluate current treatments and unmet needs of chronic inflammatory diseases with high prevalence (rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, inflammatory bowel disease, and psoriasis), and systematically review small molecules with anti-inflammatory properties presently in clinical trials for the aforementioned diseases.

As the pathophysiological knowledge of diseases increased over the last decades, a more specific intervention of inflammatory pathways becomes possible. After one hundred years of NSAIDs and over fifty years of glucocorticoids, more specific drugs for anti-inflammatory therapy such as roflumilast or fingolimod are rising. The aim of this article is to critically review the literature on small anti-inflammatory molecules in clinical trials to generate an idea of what we can expect in the future.

Contents

Abbreviations: 5-LO, 5-lipoxygenase; AA, arachidonic acid; b.i.d, bis in die (twice a day); CCR, CC chemokine receptor; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; CRTh2, chemoattractant homologous receptor expressed on Th2 cells; DHODH, dihydro-orotate dehydrogenase; DMARD, disease-modifying antirheumatic drugs; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IFN, interferon; IKK, IκB kinase; IL, interleukin; JAK, janus kinase; KEAP1, Kelch-like ECH-associated protein 1; LEF, leflunomide; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; mPGES-1, microsomal prostaglandin E_2 synthase-1; MS, multiple sclerosis; MTX, methotrexate; nAChR, nicotinic acetylcholine receptor; NE, neutrophil elastase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRF2, nuclear factor (erythroid-derived 2)-like 2; NSAID, non-steroidal anti-inflammatory drug; OxPL, oxidized phospholipids; P2X7, purinergic receptor P2X, ligand-gated ion channel, 7; PDE4, phosphodiesterase 4; PPAR, peroxisome proliferator-activated receptor; RA, rheumatoid arthritis; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; SEGRA, selective glucocorticoid receptor agonist; STAT, signal transducers and activators of transcription; SYK, spleen tyrosine kinase; TNF, tumor necrosis factor; TLR, toll-like receptor; UC, ulcerative colitis; VLA-4, very late antigen-4.

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1. Introduction

Drugs for the relief of pain, fever, and inflammation have been known for centuries, and the history of anti-inflammatory drugs is an impressive example of successful drug development. Many of these agents have their origin in extracts or decoctions of plants such as willow leaves or bark. Already the Assyrians have used the extract of willow leaves for the reduction of painful conditions, and the ancient Egyptians have treated joint pain with decoctions of myrtle and willow leaves. In modern age, the extraction of salicin from willow barks by Johann Andreas Buchner in 1828 followed by the isolation and synthesis of salicylic acid by Felix Hoffmann in 1897, and finally the acetylation of salicylic acid and the birth of acetylsalicylic acid (Aspirin®) were milestones in pharmaceutical history (Jack, 1997).

Today a broad spectrum of anti-inflammatory drugs is available, which can be divided by their chemical structure into biologicals and small molecules, which include steroidal and non-steroidal agents (see Fig. 1). Despite the growing influence of biologicals especially in the autoimmune and cancer market, there is still a strong need for potent and safe small molecules. Apparently, small molecules are less expensive compared to biologicals and can usually be administered orally. The last vast reviews on anti-inflammatory drugs focused on the enormous range and type of new anti-inflammatory agents and the discovery of new therapeutic targets (Rainsford, 2007) as well as the current status of anti-inflammatory agents, with focus on anti-cytokine therapy as new anti-inflammatory strategy (Dinarello, 2010). The focus of the present review shall lie on small molecules in clinical trials for chronic inflammatory diseases, belonging to the field of immune-mediated inflammatory diseases (IMIDs), and especially to the field of autoimmune diseases (see Fig. 2).

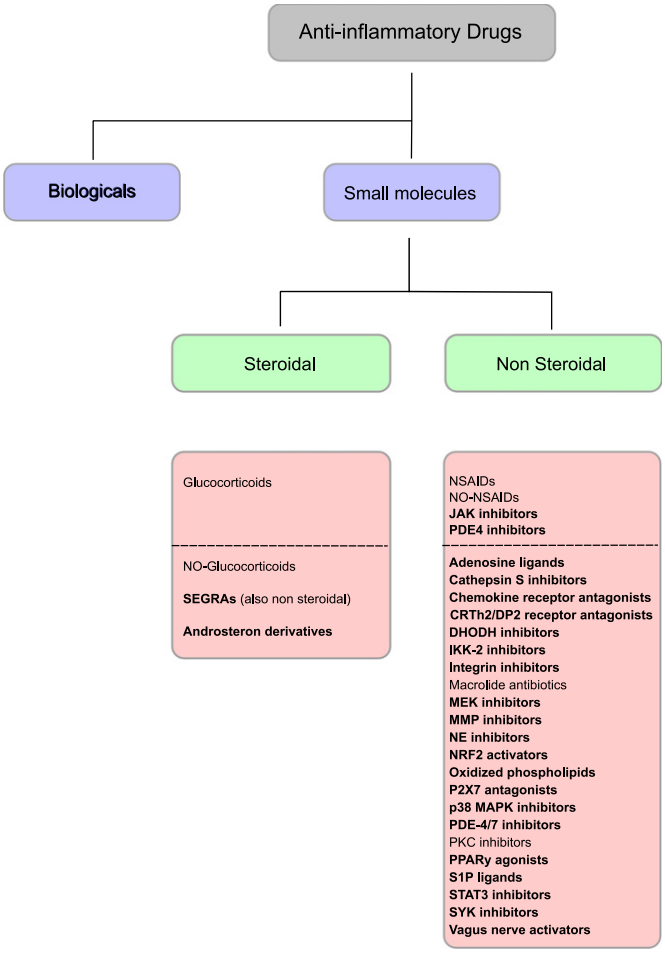

Fig. 1. Classification of anti-inflammatory drugs and overview of the drug classes that are presently evaluated in clinical trials to treat inflammatory diseases. Anti-inflammatory drugs (highlighted in grey) can be divided by their chemical structure into "biologicals" and "small molecules" (blue) that in turn can be divided into "steroidal" and "non-steroidal" agents (green). Red boxes contain an overview of drug classes with anti-inflammatory features. Above the dashed line, there are drug classes, which are already addressed by approved drugs. All drug classes in bold are addressed by agents in clinical development and will be discussed in this review.

The cellular and molecular mechanisms of an acute inflammation are widely understood (Medzhitov, 2008). In general, tissue-resident macrophages become activated by exogenous or endogenous inducers, which cause the release of inflammatory mediators. These inflammatory mediators are responsible for endothelial activation and recruitment of further effector cells to the site of inflammation. The effector cells then release their cytotoxic contents, such as reactive oxygen species (ROS) or certain types of proteases, which neutralize the cause of inflammation but at the same time damage surrounding tissue (see Fig. 3). This general mechanism of an acute inflammation is usually self-limiting through the initiation of the pro-resolution phase that prevents further recruitment and activity of effector cells and resolves the inflammatory response. However, if the acute inflammatory response fails to resolve the inflammation, chronification might follow.

In contrast to an acute inflammation, the pathomechanisms of chronic inflammation are much less understood. In particular, the triggers of chronic inflammation are not comparable to those of an acute inflammation, which is mostly caused by tissue injury or infections. Moreover, in chronic inflammation, the activation of the inflammatory cascade is often caused by a malfunction of the affected tissue and associated with a homeostatic imbalance in the physiological processes of inflammation.

The challenge to review the stage of development of anti-inflammatory drugs in clinical trials is the versatile appearance of inflammation in many diseases. Search terms such as "inflammation" or "anti-inflammatory drugs" in clinical databases would therefore have led to unsatisfactory results. For many conditions, e.g., in infectious diseases, a causal (anti-infective) therapy is available and anti-inflammatory agents are predominantly used in chronic inflammation. We will therefore focus on immune-mediated inflammatory diseases, especially autoimmune diseases, which include multiple sclerosis (MS), chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases (IBDs), psoriasis, and rheumatoid arthritis (RA) (see Fig. 2).

To systematically review clinically evaluated compounds with anti-inflammatory properties, we explored the database of the U.S. National Institute of Health, listed on clinicaltrials.gov, which we screened for the keywords rheumatoid arthritis, multiple sclerosis, psoriasis, chronic obstructive pulmonary disease, and inflammatory bowel diseases. The results were then filtered for small molecules vs. biologicals, and the molecular targets of all small molecules that are in clinical trials for one of the five mentioned diseases were evaluated for their anti-inflammatory properties. Interestingly, only a small number of the listed clinical trials were performed with small molecules with anti-inflammatory properties (about 9–17%; compare Figs. 4–8). Besides these, many clinical trials have been performed with biologicals in RA and IBD, while phototherapy has a high significance in psoriasis. For MS and COPD, there are predominantly small molecules under investigation. However, clinical trials are dominated by neuroprotective agents and vitamin (especially vitamin D) supplementation for MS