# Chapter 9

# Recent Advances in the Treatment of Immune-Mediated Inflammatory Diseases

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## Abstract

The treatment of immune-mediated inflammatory diseases (IMIDs) has dramatically improved over the last two decades by the development of a series of targeted biological therapies. This paper focuses on new developments in the treatment of IMIDs. In particular, we discuss how different ways of targeting the same mediators can lead to different efficacy and safety profiles, using B cell targeting as example. In addition, we discuss the emerging field of 'small molecules' that target specifically intracellular processes related to cytokine signaling, cell activation, cell migration, and other processes relevant to tissue inflammation.

**Key words** Immune-mediated inflammatory diseases, Treatment, B cells, Signal transduction

## 1 Introduction

Immune-mediated inflammatory diseases (IMIDs) encompasses disorders where tissue and organ inflammation is primarily driven by aberrant immune responses. In contrast to the 'secondary' involvement of the immune system in infectious diseases and oncology, the trigger of IMIDs is the immune system itself. Importantly, recent advances in our understanding of immunity and inflammation revealed that IMIDs can be driven not only by autoimmunity, defined here as abnormal responses of T and/or B lymphocytes against self-antigens, but also by auto-inflammation, this is self-directed tissue inflammation driven by aberrant or uncontrolled innate immune response triggered by local factors at tissues sites predisposed to disease. The former group encompasses diseases such rheumatoid arthritis (RA), type I diabetes, and systemic lupus erythematosis, whereas gout and sarcoidosis are examples of autoinflammatory diseases.

The treatment of IMIDs has dramatically improved over the last two decades by the development of a series of targeted biological therapies. Indeed, combined fundamental and translational immunology research has revealed that specific inflammatory

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mediators (in particular cytokines) and cells were 'master switches' in specific IMIDs and that targeting these cellular and molecular players with antibodies or soluble receptors potently down-modulated chronic inflammation. The first and major success story is TNF blockade, which is very effective to treat a variety of IMIDs including RA, spondyloarthritis (SpA), psoriasis, and inflammatory bowel disease. Other major anti-cytokine therapies are directed towards IL-1 and IL-6 and, more recently, the IL-23/IL-17 pathway. Besides targeting cytokines, a second very successful approach was to target pathogenic cell subsets, with as prime example B cell depletion with the anti-CD20 antibody rituximab. Originally developed to treat lymphomas, this compound turned out to be also very effective in the treatment of RA and other autoimmune diseases. Thirdly and finally, pathogenic cell can not only be depleted but one can inhibit their interaction with other pathogenic cells (such as in the case of co-stimulation blockade by CTLA-4-Ig or abatacept) or with molecules directing their migration into target tissues (such as the anti-alpha4 integrin antibody natalizumab).

Existing and emerging therapies targeting cytokines, cells, and cellular interactions have been extensively described in the literature and are not reviewed in detail here. This chapter rather focuses on two specific new developments in the treatment of IMIDs. Firstly, we discuss how different ways of targeting the same mediators can lead to different efficacy and safety profiles, using B cell targeting as example. We discuss novel drugs beyond rituximab that target other B cell surface molecules, other B cell subsets, and B cell growth factors. Secondly, we discuss the emerging field of "small molecules" that target specifically intracellular processes related to cytokine signaling, cell activation, cell migration, and other processes relevant to tissue inflammation.

## 2 Targeting B Cells

### *2.1 Targeting B Cells with Anti-CD20 Monoclonal Antibodies*

B cells contribute to chronic inflammatory disease by secreting cytokines, providing co-stimulatory signals to T cells, presenting antigen in the context of antibody production, and producing auto-antibodies. Therefore, selective depletion of these cells alters the immune response and reduces inflammation. Antibody-mediated depletion of B cells can be achieved via different mechanisms of which antibody-dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) are most widely used. The validity of this approach had been demonstrated by the use of the anti-CD20 antibody rituximab in RA [1] as well as ANCA-associated vasculitis [2], modest effects in SLE [3, 4], systemic sclerosis (SSc) [5], Sjogren's syndrome (SS) [6], and multiple sclerosis (MS) [7]. Rituximab is currently tested in pemphigus, AIHA, and ITP [8].

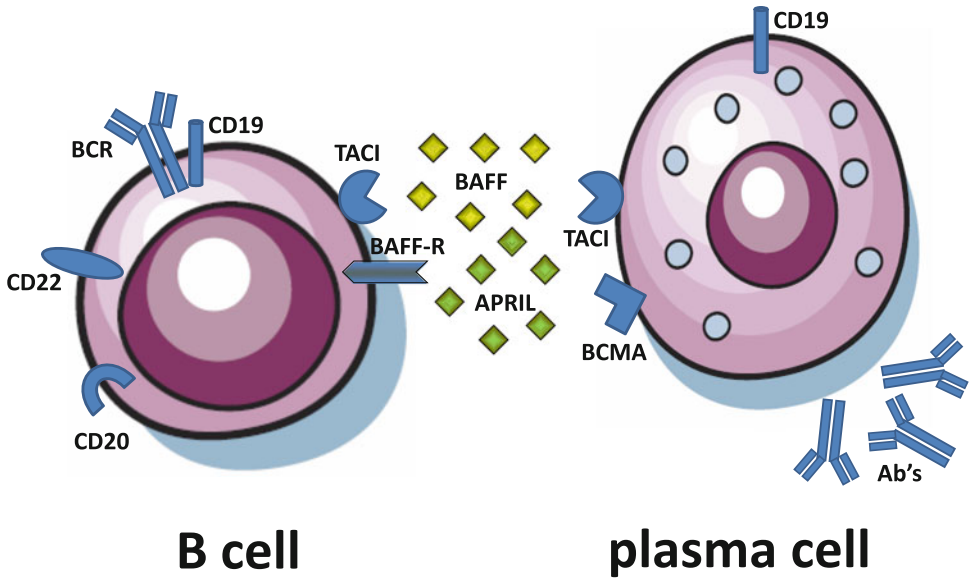


**Fig. 1** Surface molecules of B cells and plasma cells of soluble factors targeted in IMIDs. Schematic overview of B cell and plasma cell surface receptors or other molecules. The survival factors B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) bind to their respective receptors on B cells (BAFF-receptor, BAFF-R) (=TNFRSF13C), and transmembrane activator and calcium-modulating ligand interactor, TACI (=TNFRSF13B) and plasma cells (B cell maturation antigen, BCMA (TNFRSF17), and TACI. Targeting APRIL and BAFF affects both B cells and plasma cells. B cells can be targeted specifically via the B cell restricted antigens CD20 and CD22. Targeting CD19 affects both B cells, plasmablasts, and a subset of plasma cells. *Ab's* antibodies, *BCR* B cell receptor

Based on the efficacy and relatively good safety profile of rituximab (a rare but very severe complication of rituximab treatment is progressive multifocal leukoencephalopathy, a devastating demyelinating disease caused by reactivation of the JC virus [9]), other antibodies targeting CD20 are currently in development with the aim to improve the efficacy and safety profile (Fig. 1).

*Ofatumumab* is a fully humanized IgG1 mAb which binds a CD20 epitope distinct from the binding site of rituximab. Ofatumumab has enhanced CDC activity compared to the other anti-CD20 mAbs [10]. In RA data from initial phase 1/2 and 3 studies point towards favorable effects on disease activity [11, 12]. In a phase 2 dose-finding study in MS ofatumumab treatment resulted in a substantial reduction in new and total lesions [13].

*Ocrelizumab* is a humanized anti-CD20 mAb that binds a different but overlapping epitope from rituximab. It has similar CDC, but 2–5-fold increased ADCC [14]. Overall, it appears that fewer anti-drug antibody responses are elicited during ocrelizumab treatment. In RA patients ocrelizumab treatment resulted in reduced disease activity and a reduction in joint damage, however this was accompanied by an increased risk of infections which led to termination of development for RA [15, 16]. In SLE nephritis, overall renal response rates with ocrelizumab were numerically but not

statistically significantly superior to those with placebo, while ocrelizumab treatment was associated with a higher rate of serious infections in the subgroup receiving background MMF [17]. Nevertheless, in MS after initial favorable results [18], additional clinical trials in different forms of this disease are still ongoing.

*Veltuzumab* is a humanized IgG1 anti-CD20 mAb with both structural and functional differences from rituximab. It has shown promising clinical activity in relapsing ITP [19] and is also being evaluated for RA [20], but no results have been disclosed yet.

### 2.2 Targeting Other B Cell Surface Molecules

CD19 is a B cell-restricted antigen that regulates the threshold for B cell activation and, in contrast to CD20, is maintained on plasmablasts and subsets of plasma cells (Fig. 1) [21]. Therefore, targeting CD19 is expected to have a more profound effect than anti-CD20 therapy [22]. MEDI-551 is a humanized IgG1 afucosylated mAb targeting CD19 with enhanced ADCC effector function [23]. It is currently under evaluation in clinical trials for systemic sclerosis (SSc) (Clinical Trials.gov: NCT00946699) and MS [24].

CD22 is considered to be a B cell antigen (expressed on the majority of $IgM^+IgD^+$ B cells, but less so on germinal center B cells and plasma cells), which can also be detected on basophils and dendritic cells (Fig. 1) [25]. However, CD22 has been demonstrated to play an important role in the control of B cell activation, B cell survival, and cell-cycle progression following activation [26]. Epratuzumab is a humanized IgG1 mAb directed against CD22 with modest ADCC, but no CDC activity (most likely due to rapid internalization of CD22 after Ab binding) [27]. In an open-label phase 1/2 study in Sjogren's syndrome (SS) epratuzumab treatment was well-tolerated and resulted in a moderate clinical responses [28]. A phase 2 study in SLE patients also demonstrated favorable clinical effects [29, 30]. Phase 3 trials in SLE are currently ongoing.

### 2.3 Targeting B Cell Survival Factors

Besides targeting B cell themselves, a novel strategy consists of targeting B cell growth and survivial factors. Indeed, B cell function and survival depends on various factors of which the TNF family members B-cell activating factor (BAFF or BlyS) and a proliferation induced ligand (APRIL) are probably most important in the context of autoimmune diseases. Interestingly, BAFF and APRIL also support plasma cell survival (Fig. 1) [31].

Belimumab is a fully human IgG1 mAb that selectively inhibits BAFF, which results in B cell apoptosis [32]. It is effective in SLE in patients with active, autoantibody positive disease [33] and was approved by the EMA and FDA for this indication in 2011. Belimumab was not very successful in RA [34], however its efficacy is currently under investigation for ITP, Waldenstrom's macroglobulinemia, idiopathic membranous glomerulonephropathy, Sjogrens syndrome (SS), prevention of kidney transplant rejection, and myasthenia gravis (reviewed in [35]).

Tabalumab is a humanized IgG4 antibody that binds and neutralizes both soluble and membrane-bound BAFF [36]. A phase 2 dose-ranging study of subcutaneous tabalumab for the treatment of active RA patients with an inadequate response to methotrexate was successful [37]. Clinical trials in SLE [38] and MS [39] are ongoing, but results have not been published yet.

Atacicept is a fusion protein soluble receptor construct of Transmembrane Activator and Calcium-modulating ligand Interactor (TACI) and the Fc part of human IgG1 (TACI-Ig) [40]. TACI is a receptor that is normally expressed both on B cells and on plasma cells and binds both BAFF and APRIL [41]. It has been tested in SLE [42] and RA [43, 44], but in general was not successful. In MS atacicept even worsened disease activity [45]. One explanation for this may be that atacicept also targets survival factors for regulatory B cells without full depletion of pathogenic B cells [46]. This example as well as the other emerging biological drugs discussed above in the context of B cell targeting illustrate well that different ways of approaching a therapeutic target can result in strongly different efficacy and safety profiles.

## 3 Targeting Intracellular Signaling Pathways

Besides novel approaches to target extracellular molecules (including cytokines, growth factors, surface markers, co-stimulatory molecules, and adhesion molecules), intense efforts have been made in the last years in identifying intracellular targets, since all inflammatory responses are initiated by activation of intracellular signal transduction pathways. Examples of key molecules in these intracellular pathways are mitogen-activated protein kinases (MAPKs), nuclear factor-kappaB (NF-κB) activating kinases, Janus kinase (JAK), spleen tyrosine kinase (Syk), and phosphoinositide 3′kinase. Here we discuss the advances in targeting MAPKs, NF-κB, and JAKs as examples.

### *3.1 Targeting MAPK*

The family of mitogen-activated protein kinases (MAPKs) play a central role in the regulation of various biological processes that are involved in immune responses, such as proliferation, differentiation, pro-inflammatory gene expression, and survival. MAPKs are activated in response to environmental stress factors, such as TLR ligands, cytokines, growth factors, and radiation. Subsequently, MAPKs induce signaling by phosphorylating specific target proteins. MAPKs consist of three main groups that all have specific roles in the regulation of cell function: p38 MAPKs, extracellular signal-regulated protein kinases (ERKs), and c-jun $NH_2$ terminal kinases (JNKs). Recently, several additional atypical MAPKs such as ERK5, ERK3/4, ERK7/8, and Nemo-like kinase have been described [47], but these are less well studied and are not discussed here.

#### 3.1.1 p38 Inhibitors

p38 has four isoforms (α, β, γ, and δ), of which p38α and p38β are ubiquitously expressed. Activation and phosphorylation of p38 is regulated by the upstream MAPK kinases (MKK)3 and MKK6 that are phosphorylated by multiple MKK kinases (MAP3Ks). Particularly p38α is a signaling molecule that regulates pro-inflammatory cytokine production (such as TNFα, IL-1β, and IL-6), which makes it an attractive target for many IMIDs including RA. Consequently, intense efforts have been made to develop small molecule p38 inhibitors. However, despite being effective in preclinical models of arthritis, to date clinical trials in RA have all failed due to poor efficacy or toxicity, including hepatotoxicity (reviewed in [48]). Yet, in inflammatory bowel disease (IBD) initial clinical trials with the p38 inhibitor Semapimod (CNI-1493) appeared promising [49] and follow-up studies have established a mild beneficial effect in a limited number of patients [50]. A potential explanation for these rather disappointing results may lie in the fact that p38 also has anti-inflammatory effects or that blocking one kinase may lead to compensatory effects in other kinases that regulate the same genes. Therefore, an alternative more effective strategy may be to block upstream kinases such as MKK3/6 [48].

#### 3.1.2 ERK Inhibitors

The ERK family consists of two conventional MAPK, namely ERK 1 and ERK2, that are activated by the MAPKKs MEK1 and MEK2 in response to growth factors, including platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). ERK1 and ERK2 are important for cell proliferation and differentiation [47]. FR180204, an ERK inhibitor, has been shown to be effective against mouse collagen-induced arthritis, a representative animal model of RA. The MEK1/2 inhibitors PD98059 and U0126 are not competitive with respect to ATP, but appear to physically interact with MEK1/2 thereby preventing phosphorylation and/or conformational transition that generates the activated enzyme. More recently, additional noncompetitive inhibitors of MEK1/2 with greater bioavailability (PD184352 and PD0325901) have been developed and entered clinical trials as potential anticancer agents (reviewed in [47]). However, no clinical trials in IMIDs have been performed so far.

#### 3.1.3 JNK Inhibitors

The three JNK isoforms (JNK1, JNK2, and JNK3) are involved in many processes that contribute to chronic inflammation such as matrix metalloproteinase (MMP) and cytokine production, cell migration, and angiogenesis [51, 52]. JNK1 and JNK2 are widely expressed, and therefore most attention of pharmaceutical companies has gone out to target these isoforms [51]. SP600125, a direct inhibitor of JNK activity, decreased paw swelling in rat adjuvant-induced arthritis, which was accompanied by a near-complete inhibition of radiographic damage [53]. However, this inhibitor lacked specificity and was replaced by more selective inhibitors.

At present, several companies have JNK inhibitors that are in different stages of development, but no data of clinical trials in IMIDs have been reported.

### 3.2 NF-κB Inhibitors

The Nuclear Factor-kappaB (NF-κB) family of transcription factors is crucially involved in the regulation of immune responses in IMIDs (reviewed in [54]). NF-κB can be activated via two distinct pathways: the canonical pathway and the alternative or noncanonical pathway. The canonical pathway is most extensively studied and can be activated by stimulation of a variety of cell membrane receptors including tumor necrosis factor receptor (TNF-R), IL-1 receptor, and Toll-like receptors, in response to their respective pro-inflammatory ligands, as well as via triggering of classic immunoreceptors like the T-cell receptor (TCR) or the B-cell receptor (BCR). In this pathway, inhibitor of κB (IκB) kinase (IKK)β is required for NF-κB activation, whereas IKKα is redundant (reviewed in [55]). The canonical NF-κB pathway is essential both in acute inflammatory responses and in chronic inflammatory diseases such as RA and inflammatory bowel disease [56]. In RA IKKβ is a key regulator of synovial inflammation and the importance of the canonical NF-κB pathway in arthritis is underlined by the beneficial effects of specific IKKβ inhibition in preclinical models of arthritis [57, 58]. Fuelled by these results and beneficial effects of NF-κB inhibition in preclinical models of other inflammatory diseases, more than 700 compounds with inhibitory effects on NF-κB signaling have been reported [59]. However, clinical trials are hitherto lacking, presumably by fear of toxicity associated with global NF-κB inhibition or off-target effects. This could potentially be solved by selective targeting of the NF-κB inhibitor to a specific cell type, for instance using a multimodular recombinant protein that specifically binds to cytokine-activated endothelium, which has been demonstrated to work very elegantly under inflammatory conditions in vivo [60].

The noncanonical NF-κB pathway can be triggered by the activation of members of the TNF-receptor superfamily including the lymphotoxin β receptor (LTβ-R), CD40, B cell activating factor belonging to the TNF family (BAFF) receptor, and receptor activator of NF-κB (RANK). Of note, these receptors not only trigger the noncanonical NF-κB pathway, but simultaneously also the canonical pathway. The noncanonical NF-κB pathway is strictly dependent on NF-κB inducing kinase (NIK) and IKKα homodimers, but does not involve IKKβ or IKKγ. Overall, this pathway is involved in lymphoid organ development and adaptive immune responses [61]. Recently, we established that noncanonical NF-κB signaling in endothelial cells stimulates pathological angiogenesis in chronic inflammation [62]. Consequently, NIK inhibition using specific small molecule inhibitors could perhaps be an effective new treatment option for chronic inflammatory diseases [63].

### 3.3 Janus Kinase (JAK) Inhibitors

The Janus kinase (JAK) family consists of four members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAKs associate with different cytokine receptors and via phosphorylation of tyrosine residues create docking sites for one or more signal transducer and activators of transcription (STAT) molecules. JAK1, JAK2, and TYK2 are ubiquitously expressed, whereas JAK3 is primarily expressed in hematopoietic cells. JAK1 and JAK3 convey signals from cytokine receptors that contain the IL-2 receptor common γ chain and mediate signaling by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, cytokines that are essential for the development and maturation of T cells. JAK2 is associated with hematopoietic growth factor receptors and cytokine receptors for IL-1, IL-6, and IL-17 that are critically involved in various aspects of immune cell function (reviewed in [64]). Consequently, inhibiting JAKs blocks multiple aspects of cytokine signaling, which makes them attractive targets for many IMIDs. Of all protein kinase inhibitors, JAK inhibitors have entered the clinic first. Tofacitinib (also known as CP-690550) is a potent JAK1 and JAK3 blocker, that also inhibits JAK2 to a certain extent. It was effective in preclinical models of arthritis and transplantation [65, 66]. Tofacitinib successively entered clinical trials, which demonstrated efficacy in RA [67, 68], IBD [69], and psoriasis [70]. In 2012 tofacitinib was approved for the treatment of RA in the USA, Japan and Russia. However, the European Medicines Agency (EMA) did not approve tofacitinib for RA, mainly due to concerns about the risk of serious infections. Nevertheless, EULAR included tofacitinib in their recommendations for the treatment of RA as a therapeutic option after biological treatment has failed [71].

## 4 Conclusion

The treatment of IMIDs continues to improve as we develop a better understanding of the pathogenesis of these diseases and the pathways that are suitable for targeting. Importantly, however, the clinical exploration of novel targeted therapies also contributes directly to our understanding of the function and role of specific pathways in vivo. This interaction between fundamental immunobiology and translational research has been key to many novel developments in the field of IMIDs.

These developments are not only related to an ongoing expansion of 'classical' target pathways (cytokines, growth factors, surface molecules, co-stimulation, adhesion) but also to fine-tuning of the way to approach these targets, as discussed for B cells. The key message here is that a single pathogenic pathway may operate in completely different ways depending on the exact immunological and tissue context. As we discussed recently for another key inflammatory pathways, the IL-23/IL-17 axis, studying the context of

inflammation is as important as understanding the pathway to determine how, when and where this pathway should be optimally targeted [72, 73].

This may be further improved by new developments in recombinant antibody technology allows for the generation of bispecific antibodies that have the ability to bind to two different epitopes on the same or different antigens. This may have significant advantages over targeting one epitope, especially in complex multifaceted diseases [74], since with a single therapeutic entity two targets can be blocked or engaged. This approach has been rapidly adopted by the oncology and hematology field, and attempts are also made in the field of clinical immunology and rheumatology. An example of this is a bispecific hexavalent antibody comprising epratuzumab and veltuzumab (anti-CD22/CD20), which may lead to improved treatment of SLE and other IMIDs, but has not been formally tested yet [75].

Finally, new horizons are opening with completely novel targets such as the intracellular signaling pathways. This review discussed a few examples in order to highlight the enormous progresses and promises ahead of us, but is obviously far from complete. For example, there is crucial emerging knowledge in the role of epigenetic modifications in the initiation and maintenance of tissue inflammation and, accordingly, small molecules modifying for example DNA methylation and histone modifications are in (pre)clinical development [76]. To date, one clinical trial with a histone deacetylase (HDAC) inhibitor has been performed in systemic juvenile inflammatory arthritis. Oral administration of the nonselective HDACi givinostat (ITF2357) resulted in significant therapeutic benefit after 12 weeks, particularly with respect to arthritis activity, with a relatively good safety profile [77]. These and other new developments will continue to revolutionize the treatment of IMIDs and contribute to the ongoing evolution from nonspecific immune suppression to targeted immunomodulation and, ultimately, genuine disease modification and cure.

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