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Corticosteroid, Other Biologic and Small Molecule Therapies in Systemic Autoinflammatory Disorders

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Abstract

Not all patients with autoinflammatory disorders respond to treatment with colchicine or anti-interleukin (IL)-1 agents. Although no other biologics nor small molecule pharmaceuticals are currently licenced for use in autoinflammatory disease several agents are used. The pharmacology, mechanisms of action and safety data of these medications are summarised in this chapter. These include corticosteroids, tumor necrosis factor (TNF), IL-6 and Janus kinase (JAK) inhibitors. There are published consensus criteria which provide guidance to the management of familial Mediterranean fever (FMF), cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor receptor associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD).

Keywords

Corticosteroids · Monoclonal antibodies
Etanercept · Infliximab · Adalimumab
Interleukin-6 · Tocilizumab
Janus kinase inhibitors · Baricitinib
Tofacitinib

Abbreviations

CANDLE	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	Cryopyrin-associated periodic syndromes
CAR	Chimeric antigen receptors
CNO	Chronic non-bacterial osteomyelitis
CRP	C-reactive protein
DADA2	Deficiency of adenosine deaminase 2
FDA	Food and Drug Administration
FMF	Familial Mediterranean fever
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GTI	Glucocorticoid Toxicity Index
IL	Interleukin
INF	Interferon
JAK	Janus kinase
MKD	Mevalonate kinase deficiency
NF-κB	Nuclear factor kappa B
NLRP	Nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAPA	Pyogenic arthritis, pyoderma gangrenosum, acne
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis
SAA	Serum amyloid A
SAVI	STING-associated vasculopathy with onset in infancy

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SHARE	Single Hub and Access point for Paediatric Rheumatology in Europe
SOSC	Suppressor of cytokine signaling
STAT	Signal transducer and activator of transcription
TNF	Tumor necrosis factor
TRAPS	Tumor necrosis factor receptor-associated periodic syndrome
TYK	Tyrosine kinase
UK	United Kingdom
USA	United States of America

Key Points

- **Not all autoinflammatory disorders respond to modulation of the interleukin (IL)-1 pathway**
- **There are published consensus criteria for the management of familial Mediterranean fever (FMF), cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD)**
- **No other biologics or small molecule pharmaceuticals are currently labelled for use in autoinflammatory disease**
- **Biologics must be given parenterally and are prohibitively expensive; novel approaches currently being explored include drug repurposing and development of inflammasome inhibitors**

42.1 Introduction

A remarkable feature of the autoinflammatory diseases has been the almost complete responses seen once the appropriate treatment is started. The dramatic responses to colchicine in familial Mediterranean fever (FMF) and anti-interleukin (IL)-1 therapies in cryopyrin-associated periodic syndromes (CAPS) and tumor necrosis factor receptor associated periodic syndrome (TRAPS) have been covered elsewhere (see Chaps. 40 and 41) but these agents are not a complete panacea. The experience of other therapies which help with the management of these disorders and their pharmacology, mechanisms of action and safety data are summarised in this chapter. Treatment of systemic autoinflammatory diseases is a rapidly moving field and it is likely that our armamentarium will expand to include newer biologics targeting other cytokines, for example interferon (IFN) γ, IL-17 (secukinumab), IL-12/23 receptor (ustekinumab), novel agents designed to specifically target autoinflammatory pathways and repurposed old drugs.

42.2 Corticosteroids

- **The only indication for corticosteroids in familial Mediterranean fever (FMF) is prolonged febrile myalgia**
- **In other autoinflammatory diseases short-term corticosteroids can be effective in terminating acute inflammatory attacks**
- **Long-term use of corticosteroids should be avoided due to the high risk of serious adverse effects**

Corticosteroids are among the most widely used anti-inflammatory drugs and 1% of the population of the United States of America (USA) is estimated to be taking them at any time [1]. Their ability to down regulate expression of multiple genes involved in inflammatory pathways (including those encoding cytokines and chemokines, their receptors, adhesion molecules, inflammatory enzymes) have proved useful in autoinflammatory disorders, including many such as gout, chronic non-bacterial osteomyelitis (CNO), systemic juvenile idiopathic arthritis and Behçet disease which are discussed elsewhere in this book (see Chaps. 31, 32, 34, 35). Corticosteroids have been given as both short-term and, more problematically, long-term therapy and via oral and parenteral routes [2].

42.2.1 Mechanisms of Action

The anti-inflammatory effect of cortisol was first recognised by Hench in patients with coincidental Cushing syndrome and rheumatoid arthritis in 1949 [3]. The mechanisms of action of corticosteroids are complex, wide-ranging and remain incompletely understood. They undoubtedly affect gene expression; corticosteroids are taken up intracellularly and bind to cytoplasmic receptors. The resultant receptor-steroid complex migrates into the nucleus, binds to DNA and over a period of a few hours to a day or so alters protein synthesis. Many of these effects are mediated by transrepression with inhibition of the effect of proinflammatory transcription factors such as nuclear factor kappa B (NF-κB) or by reducing or reversal of deacetylation of acetylated histones [4]. Other effects result from upregulation of genes with anti-inflammatory functions such as mitogen-activated protein kinase phosphatase-1, IL-10, and corticosteroid-induced leucine zipper, an inhibitor of NF-κB. In addition corticosteroids can have non-genomic actions which may be apparent more rapidly. These are thought to be mediated by membrane-coupled receptors and have been reported to inhibit neutrophil degranulation and appear to contribute to some of their neuropsychiatric side effects [5].

Table 42.1 Significant adverse effects associated with long-term corticosteroid therapy

Skin Thinning and striae Purpura Acne Hirsutism Increased risk of squamous cell and basal cell carcinoma Cushingoid appearance: Moon face, buffalo hump, truncal weight gain	**Immune response** Increased risk of infection, particularly atypical or opportunistic Increased risk of herpes zoster reactivation Reduced response to vaccination
Ocular Posterior cataracts Glaucoma	**Renal** Fluid retention Hypertension Hypokalaemia
Metabolic Insulin resistance Abnormal lipid metabolism Central obesity Accelerated atherosclerosis and increased risk of cardiovascular events	**Central nervous system** Hypomanic symptoms Depressive symptoms Akathisia Insomnia Psychosis (at high doses)
Musculoskeletal Myopathy - typically proximal Osteoporosis Osteonecrosis	Growth retardation (in children)
Gastrointestinal Gastritis, peptic ulcers and bleeding Visceral perforation	**Endocrine** Diabetes mellitus Suppression of hypothalamic-pituitary-adrenal axis

42.2.2 Adverse Effects

Unfortunately, long-term use of systemic corticosteroids carries a serious risk of significant, poorly reversible adverse effects which limit their use particularly at doses of more than 10 mg/day in adults and for more than a few months [6, 7]. These range from suppression of the hypothalamic-pituitary-adrenal axis leading to adrenal atrophy, to an increased risk of cardiovascular events, metabolic syndrome with weight gain, abnormal glucose tolerance and development of diabetes, infections, gastrointestinal bleeding and perforation, myopathy, osteoporosis and cataract formation (Table 42.1). Some of the metabolic consequences are thought to be due to transactivation of a variety of genes involved in carbohydrate, lipid and protein metabolism following binding to corticosteroid response elements whereas the increased risk of infection seems to be due to transrepression, and osteoporosis to a combination of both, resulting in decreased transcription of osteocalcin and increased osteoblast apoptosis. Genetic polymorphisms in pathways involving steroid metabolism, steroid receptors, and transport proteins have been suggested to have an important role in the development of corticosteroid-induced adverse effects.

Attempts to define the incidence and burden of corticosteroid adverse effects have been limited perhaps because the adverse profile of an affordable group of drugs, which have been in

widespread use for many decades, has become too broadly accepted [8]. A Glucocorticoid Toxicity Index (GTI) has recently been developed by a group of clinicians representing multiple specialities including pediatricians and adult physicians utilising multi-criteria decision analysis [9]. This generates a weighted score from a series of domains (body mass index, glucose tolerance, blood pressure, lipids, bone density, steroid myopathy, skin, neuropsychiatric problems, infection, endocrine, gastrointestinal, musculoskeletal and ocular toxicity) which were felt not to be confounded by comorbidity or life style, to assess the burden of corticosteroid adverse effects and changes over time.

42.2.3 Use of Corticosteroids in Familial Mediterranean Fever (FMF)

The only widely accepted use of corticosteroids in FMF is for the treatment of protracted febrile myalgia (see Chap. 16). This rare complication of FMF was first described in 1994 and seems more common in patients homozygous for the severe M694V mutation. It presents as a prolonged (4–6 weeks) episode of muscle pain affecting the limbs, without rhabdomyolysis, and a marked systemic inflammatory response. Treatment is usually with non-steroidal anti-inflammatory drugs (NSAIDs) or oral corticosteroids [10] and a comparative study suggested equal efficacy [11]. A 2017 study reported a rapid response to intravenous pulse corticosteroids (methylprednisolone) at a dose of 10 mg/kg followed by oral corticosteroids tapered over 6 weeks [12].

42.2.4 Use of Corticosteroids in TNF-Receptor Associated Periodic Fever Syndrome (TRAPS)

Corticosteroids are widely used to terminate acute attacks of TRAPS (see Chap. 18) but data come from small retrospective studies only [13–15]. Treatment is generally reported to be effective in terminating attacks but episodic treatment does not reduce the frequency of attacks. Some centres have reported using intravenous methylprednisolone, but this is not widespread [14]. Long-term corticosteroids have been used in patients refractory to other treatment but are associated with severe adverse effects. Data from the Eurofevers/Eurotraps registry demonstrate that corticosteroids were completely effective in terminating acute attacks in 42% of 48 cases and partially effective in a further 52% [16]. Most patients require doses of between 0.5 and 1 mg/kg/day to control symptoms. Intermittent corticosteroids do not prevent subsequent symptomatic attacks, nor subclinical inflammation between attacks. Almost 80% of patients initially treated with corticosteroids were converted to maintenance therapy with a specific cytokine blocking therapy.

Consensus recommendations for the management of autoinflammatory diseases were developed as part of the European project Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) and published in 2015 [17]. These recognise that short-term corticosteroids, with or without NSAIDs, are effective for terminating inflammatory attacks but that their beneficial effect can decline over time so that increasing doses are required to achieve an equivalent response.

Our practice is to use short, less than 2 week, courses of prednisone at doses of 0.5–1 mg/kg/day to manage intermittent acute attacks with a rapid reduction in dosage as symptoms remit. Long-term maintenance corticosteroids are not used due to the high risk of adverse effects. Prompt conversion to biologic therapy is indicated when disease is refractory to corticosteroids; or relapses rapidly after corticosteroid withdrawal; or requires frequent doses of corticosteroids with a cumulative dose approaching 7 mg/day/annum in adults; or exhibits subclinical biochemical evidence of inflammation between attacks.

42.2.5 Use of Corticosteroids in Mevalonate Kinase Deficiency (MKD)

Corticosteroids are used in acute attacks of mevalonate kinase deficiency (MKD) in a very similar way to their use in TRAPS (see Chap. 17). In the

Eurofever registry, corticosteroids were used in 49 of 114 (43%) patients to treat fever attacks. Complete suppression of inflammatory episodes was reported for 19 (39%) (16 of whom had not received biologics), and some improvement was reported for 21 (43%) patients. Five of seven patients who received maintenance corticosteroids experienced some benefit [16]. Other older series also suggest the response to corticosteroids are often disappointing in the longer term [18].

42.2.6 Use of Corticosteroids in Idiopathic Recurrent Pericarditis

Corticosteroids are often used as symptom control and to shorten attacks of idiopathic recurrent pericarditis but there has been longstanding concern that they increase the risk of recurrent attacks [19] (see Chap. 36). The results of colchicine trials in prophylaxis of recurrent pericarditis support this concern [20]. Current advice is that corticosteroids should be used only after failure of aspirin/NSAID and colchicine [21]. Prednisolone doses of 0.25–0.5 mg/kg/day for 4 weeks followed by slow tapering have been recommended. Recurrences are common below doses of 10–15 mg/day and are difficult to manage. In patients requiring unacceptably prolonged or high doses of corticosteroids prompt introduction of alternative immunosuppressive or anti-cytokine therapy should be considered [21].

42.2.7 Use of Corticosteroids in Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis (PFAPA) Syndrome

A diagnostic feature of periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome is the dramatic and rapid response to a single dose of oral corticosteroids [22] (see Chap. 30). Prednisolone doses of 0.5–2 mg/kg have been used with similar efficacy [23]. A rapid resolution of fever, within 12–24 h, has been reported in 63% of cases and only 5% show no response [24]. The major downside of using corticosteroids in PFAPA is that they do not prevent further attacks and the interval between episodes may be shortened in 25–50% of cases. If corticosteroids are used very frequently there is a risk of cushingoid side effects, otherwise adverse effects are rare; restlessness is the most commonly reported [25].

42.2.8 Use of Corticosteroids in Deficiency of Adenosine Deaminase 2 (DADA2)

Treatment of deficiency of adenosine deaminase 2 (DADA2) has so far only been reported in retrospective case series (see Chap. 23). High dose corticosteroids appear highly effective at controlling disease activity in DADA2 in the short term. However, in a multicentre series, all patients with chronic disease relapsed as the dose of corticosteroids was reduced. Indeed, if used as monotherapy, corticosteroid tapering carries a risk of severe complications such as cerebrovascular accident and intussusception [26].

42.3 Anti-Tumor Necrosis Factor (TNF) Agents

- **In systemic autoinflammatory diseases etanercept and anti-TNF antibodies may have different effects**
- **Etanercept is beneficial in some cases of TRAPS whereas anti-TNF monoclonal antibodies should be avoided**
- **In Blau syndrome response to TNF blockade appears variable but anti-TNF antibodies may be a better choice of agents than etanercept**
- **Anti-TNF agents are widely used to treat DADA2**

Tumor necrosis factor (TNF)-α is a cytokine with pleiotropic effects including both proinflammatory and immune regulatory functions. Its activities are mediated via interaction with two distinct cell surface receptors, p55/TNFRI and p75/TNFRII with separate signal transduction pathways. The receptors are expressed on the majority of cells and

the binding of both the membrane-bound and soluble forms of TNF (sTNF) results in inflammatory responses. These may be cell type specific including enhanced cytotoxicity, T-cell and macrophage migration, granuloma formation, IL-10 production, B cell proliferation and immunoglobulin production, T cell HLA-DR and CD25 expression and granulocyte-macrophage colony-stimulating factor (GM-CSF) production [27].

There are currently five anti-TNF agents labelled for use in humans: etanercept (and biosimilars), infliximab (and biosimilars), adalimumab (and biosimilars), golimumab and certolizumab (Table 42.2). Although all five agents target TNF, etanercept is a receptor analogue and the others are monoclonal antibodies. Etanercept appears to induce less T cell apoptosis than infliximab but inhibits signalling by lymphotoxin-α. Lymphotoxin-α is a key cytokine in the regulation of the mucosal immune system and its inhibition may contribute to the relative lack of effect of etanercept in inflammatory bowel disease. Differences between agents certainly seems to have clinical significance in TRAPS. The adverse event profile also varies subtly particularly with respect to the risk of developing tuberculosis. The lower (although real) risk with etanercept may reflect lesser inhi-

Table 42.2 Comparison of labelled anti-tumor necrosis factor (TNF) agents

	Etanercept (ETA)	Infliximab (INF)	Adalimumab (ADA)	Golimumab (GOL)	Certolizumab (CER)
Structure	Human fusion protein of two TNFR2 receptor extracellular domains and the Fc portion of human IgG	Mouse-human chimeric monoclonal antibody	Fully human monoclonal antibody	Fully human monoclonal antibody	Humanised PEGylated Fab′ antibody fragment
Target	Trimeric soluble TNF-α, transmembrane TNF-α	Monomeric and trimeric soluble TNF-α, transmembrane TNF-α	Monomeric and trimeric soluble TNF-α, transmembrane TNF-α	Monomeric and trimeric soluble TNF-α, transmembrane TNF-α	Monomeric and trimeric soluble TNF-α, transmembrane TNF-α
Route of administration	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous or intravenous	Subcutaneous
Standard maintenance dose in adults	50 mg	5 mg/kg	40 mg	50 mg	200 mg
Dose frequency	Weekly	Every 4–8 weeks	Every 2 weeks	Monthly	Every 2 weeks
Half-life (days)	3	9.5	14	12	14
Labelled indications	Rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, polyarthritis juvenile idiopathic arthritis	Crohn disease, ulcerative colitis, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis	Rheumatoid arthritis, polyarthritis juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn disease, ulcerative colitis, hydradenitis supperative, non-infectious intermediate, posterior and panuveitis	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

bition of T cell activation and CD4+ cells than infliximab or adalimumab. Malignancies have been a theoretical concern, although recent data, at least in adults with rheumatoid arthritis and children with chronic inflammatory diseases, including juvenile idiopathic arthritis are very reassuring [28, 29]. Other adverse effects include demyelinating syndromes, worsening of congestive cardiac failure, immunogenicity, infusion/injection reactions and hypersensitivity, hepatotoxicity and hematological disorders.

42.3.1 Use of Anti-TNF Agents in Familial Mediterranean Fever (FMF)

In general anti-TNF agents have proved disappointing in FMF. The exception is the association between FMF and both ankylosing spondylitis and sacroiliitis (see Chap. 16). In these patients, there is evidence that effective treatment of the arthritis with anti-TNF therapies may improve FMF disease control [30].

42.3.2 Use of Anti-TNF Agents in Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)

The experience of anti-TNF agents in TRAPS has generally been of limited benefit and its use has been almost entirely superseded by far more effective anti-IL-1 agents (see Chap. 18). TNF antibodies are contraindicated as they have been reported to worsen disease. A possible molecular mechanism for this phenomena has been proposed, wherein failure to shed infliximab-bound TNF/TNFRI from the cell surface triggers enhanced anti apoptotic c-Rel activation, and increased secretion of pro-inflammatory cytokines [31].

The soluble TNF receptor fusion protein, etanercept, was widely used in TRAPS. Multiple case reports in the early 2000s had suggested that more than 80% of patients had a response to initial treatment, of whom about 25% had a very good clinical response. A weakness of this literature was that there was very little data on using etanercept for more than a few months and loss of efficacy, potentially complicated by the development of AA amyloidosis, seemed common. An open-label study of etanercept in 15 patients reported a partial response over 14 weeks in terms of symptoms and to a lesser extent a decrease in acute phase reactants. Long-term follow-up showed a median duration of etanercept treatment of 3.3 years, which is very short for a life-long disease, with the most common reason for discontinuation being lack of efficacy. Etanercept usage was not associated with a reduction in NSAID or corticosteroid use [32].

42.3.3 Use of Anti-TNF Agents in Mevalonate Kinase Deficiency (MKD)

As with FMF and TRAPS, blockade of TNF has proved partially effective at best. In the largest published series of 114 patients, 27 received etanercept with disappointing efficacy. Only 2 (7%) had a complete response and there was no response in 11 patients (41%) [33].

42.3.4 Use of Anti-TNF Agents in Blau Syndrome

The evidence base for the treatment of Blau syndrome is extremely scanty (see Chap. 20). Although there are case reports of benefit from anti-TNF antibodies, particularly with respect to visceral granulomatous involvement, this is not clear cut in larger series [34–36]. Treatment of Blau-associated uveitis has recently been reported in 38 patients Thirty-seven (97%) were treated with systemic medication, with 68% receiving a combination of systemic corticosteroids with immunosuppressive drugs and/or biologics. Within these combinations, systemic corticosteroids were the most commonly used (68%), followed by methotrexate (47%), adalimumab (45%), infliximab (13%), mycophenolate mofetil (8%), thalidomide (5%), and canakinumab (3%). Choice of immunosuppressants varied among the participating centers, and therefore efficacy of individual agents was difficult to ascertain, but the trend over follow-up remains of cumulative worsening of visual function [37].

42.3.5 Use of Anti-TNF Agents in Deficiency of Adenosine Deaminase 2 (DADA2)

TNF blockade is the current treatment of choice in patients at risk of severe complications of DADA2 such as stroke or peripheral vascular complications. In a recently published Italian series, nine of the ten patients who received anti-TNF treatment with etanercept achieved a complete remission with a median treatment duration of 3.9 years (range 0.9–13 years); only one patient was still corticosteroid dependent [26]. In a United Kingdom (UK) series excellent responses were also seen with the anti-TNF antibodies infliximab and adalimumab [38], suggesting that the benefits of TNF blockade are not dependent on the type of agent used.

42.3.6 Use of Anti-TNF Agents in Chronic Non-Bacterial Osteomyelitis (CNO)

There are no randomized-controlled trials of treatment in chronic non-basterial osteomyelitis (CNO). TNF inhibitors have been used and there are just over 50 reports in the literature, generally in refractory disease, including the use of infliximab, adalimumab and etanercept. The majority of case reports describe benefit although the data are retrospective and follow-up generally short [39]. Consensus treatment plans were proposed in 2017 for the first 12 months of therapy for patients who have proved refractory to NSAID monotherapy and/or with active spinal lesions. One of the three options includes the use of anti-TNF agents, either alone or in combination with methotrexate [40].

42.3.7 Use of Anti-TNF Agents in Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome

There has been almost no systematic assessment of treatment efficacy in this exceptionally rare disease. Therapies targeting TNF-α including etanercept, adalimumab and infliximab have been used and case reports suggest some benefits in controlling skin and joint disease manifestations [41].

42.4 Anti-Interleukin (IL)-6 Agents

- **Experience of IL-6 blockade is largely in patients who have proved refractory to other agents**
- **IL-6 blockade can be effective and may be most useful in patients with AA amyloidosis**

IL-6 is a pleiotropic cytokine that is secreted by a range of cells including neutrophils, monocytes/macrophages, endothelial cells, fibroblasts and T-cells and plays a major role in systemic inflammation, immunity, reproduction, hematopoiesis, neural development and bone metabolism. It stimulates a number of cellular responses including proliferation, differentiation (particularly of T-cells, B-cells and neurons), survival, and apoptosis and the hepatocyte acute-phase reaction, including raised levels of C-reactive protein (CRP) and serum amyloid A (SAA) protein.

IL-6 binds to a specific receptor on target cells. The IL-6/IL6-R complex results in signal transduction by activating a homodimer of the ubiquitously expressed signal-transducing β-receptor gp130. Ligand binding results in Janus kinase (JAK), particularly JAK1, activation and phosphorylation of tyrosine residues in the intracellular portion of receptor, thereby recruiting signal transducer and activator of transcription (STAT) molecules, which are also phosphorylated by JAKs. Phosphorylated STAT translocates into the nucleus activating gene transcription (Fig. 42.1).

Regulation of IL-6 is complex and includes mechanisms to reduce cytokine signalling. One of the main negative feedback regulators of the IL-6 signalling axis is suppressor of cytokine signalling (SOCS) 3, which itself is a STAT3 target gene. SOCS3 binding to the cytoplasmic portion of gp130 and JAK, results in recruitment of an ubiquitin ligase complex and their degradation. In addition, soluble IL-6R and soluble gp130 are

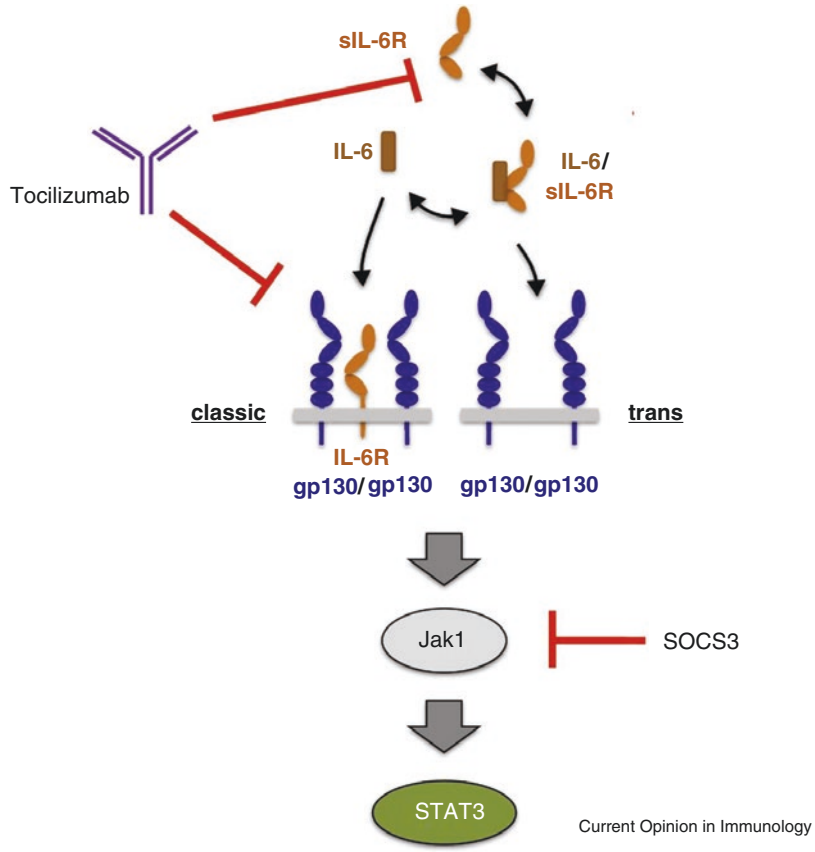

Fig. 42.1 Interleukin (IL)-6 classic and trans-signalling. IL-6 can either signal via the membrane-bound receptor (classic signalling), or in complex with the soluble IL-6 receptor (trans-signalling). Both pathways induce homodimerization of gp130 leading to the activation of intracellular signalling pathways, in particular phosphorylation of signal transducer and activator of transcription (STAT)3 via the tyrosine kinase Janus kinase (JAK)1. Negative feedback inhibition is achieved through induced expression of suppressor of cytokine signalling (SOCS3). Reproduced with permission from Garbers et al. Curr Opin Immunol 2015 [42]

present in plasma at low levels. Circulating IL-6 can bind to soluble receptor with an affinity of approximately 1 nM; this is dramatically increased by recruitment of sgp130 with the complex having a binding affinity of 10 pM. As the IL-6/sIL-6/sgp130 complex acts as an endogenous antagonist of cytokine activity it acts as an important buffer during inflammatory episodes [42].

IL-6 signal transduction can occur via membrane bound or soluble IL-6R, the former known as classic and the latter as trans-signalling. Binding of IL-6 to its membrane bound receptor appears to promote generally desirable anti-inflammatory outcomes such as healing, tissue regeneration and defence against bacterial infection. In contrast, the less desirable pro-inflammatory actions of IL-6 appear to be largely mediated via trans-signalling suggesting that its specific blockade might be beneficial. Olamkicept, a recombinant IL-6 soluble receptor antagonist, is currently in clinical trials in inflammatory bowel disease [42].

There are currently three anti-IL-6 agents labelled for use in humans: tocilizumab, sarilumab and siltuximab (Table 42.3). Tocilizumab is currently labelled by the USA Food and Drug Administration (FDA) for the treatment of: rheumatoid arthritis; systemic juvenile idiopathic arthritis; polyarthritis juvenile idiopathic arthritis; giant cell arteritis; and chimeric antigen receptors (CAR) T cell-induced (used for treatment of hematologic malignancies) severe or life-threatening cytokine release syndrome. Sarilumab is labelled at present only for the treatment of rheumatoid arthritis and siltuximab for the treatment of multicentric non-viral associated Castleman disease. The adverse event profile associated with IL-6 blocking agents includes hypersensitivity, infections including hepatitis, malignancies notably lymphoma, changes of blood counts, lipid profile, gastrointestinal perforations, deranged liver function with elevated transaminases and cardiovascular events [43, 44].

Table 42.3 Comparison of labelled anti-interleukin (IL-6) agents

	Tocilizumab	Sarilumab	Siltuximab
Structure	Recombinant humanized monoclonal antibody	Fully human IgG1 monoclonal antibody	Chimeric human-murine monoclonal antibody
Target	Both soluble and membrane bound IL-6 receptor	Both soluble and membrane-bound IL-6Rα	Both soluble and membrane bound IL-6 receptor
Route of administration	Subcutaneous	Subcutaneous	Intravenous
Standard maintenance dose in adults	162 mg	200 mg	11 mg/kg
Dose frequency for adults	Weekly	Every 2 weeks	Every 3 weeks
Half-life (days)	1.6	Initially 8–10 In steady state 21	21
Labelled indications	Systemic and polyarthritis juvenile idiopathic arthritis[a], rheumatoid arthritis, giant cell arteritis, treatment of CAR- T cell-induced cytokine release syndrome	Rheumatoid arthritis	Multicentric Castleman disease

Ig immunoglobulin; *IL* interleukin; *CAR* chimeric antigen receptors
[a]Dose for systemic juvenile idiopathic arthritis in children is 12 mg/kg intravenous administration every 2 weeks in children <30 kg and 8 mg/kg in heavier children; dose for polyarthritis juvenile idiopathic arthritis is 10 mg/kg intravenous every 4 weeks in children <30 kg and 8 mg/kg in heavier children

42.4.1 Use of Tocilizumab in Familial Mediterranean Fever (FMF)

Tocilizumab was reported to be effective in a Japanese patient with colchicine-resistant FMF complicated by recurrent fasciitis and myositis [45] and in number of cases of FMF complicated by AA amyloidosis (see Sect. 42.4.4).

42.4.2 Use of Tocilizumab in Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)

One patient with a cysteine mutation who had failed to respond to etanercept and had a partial response to anakinra (recombinant IL-1 receptor antagonist), complicated by the development of neutropenia, was treated with tocilizumab with a good clinical and biochemical response, sustained over 6 months of follow up [46].

42.4.3 Use of Tocilizumab in Mevalonate Kinase Deficiency (MKD)

MKD is often difficult to treat with disappointing responses. Although current data suggest IL-1 blockade is probably the most effective current therapy, there are several reported cases describing the use of tocilizumab in treatment refractory cases with encouraging responses [47–50] (Table 42.4).

42.4.4 Use of Tocilizumab in AA Amyloidosis

Tocilizumab has been reported to be effective in patients with AA amyloidosis complicating FMF, MKD and uncharacterised autoinflammatory diseases. Many of these patients had long-standing severe disease resistant to conventional therapies. In AA amyloidosis the major aim of treat-

Table 42.4 Summary of case report use of tocilizumab in mevalonate kinase deficiency (MKD)

	Shendi et al. [47] (n = 1)	Stoffels et al. [48] (n = 2)		Lane et al. [49] (n = 2)		Muster et al. [50]
Patient	**1**	**2**	**3**	**4**	**5**	**6**
Tocilizumab dose (mg/kg) and route of administration	7 IV	8 IV	8 IV	8 IV	8 IV	8 IV
Frequency of administration (weeks)	4	4	4	4	4	4
Age at onset of treatment (years)	13	Not described	Not described	24	13	36
Treatment prior to tocilizumab	Colchicine, prednisolone, etanercept, anakinra	Anakinra	Anakinra	Anakinra, etanercept	Etanercept	NSAID, simvastatin, anakinra
Duration of treatment (months)	20	5	5	24	13	48–60
Clinical outcome	CR	CR	CR	CR		PR
Serologic outcome	CR	Not described	PR	CR		PR
Adverse events	URI	Not described	Not described	Not described		Not described
Comments	CR at dose of 8 mg/kg but due to AE dose halved; subsequently increased inflammatory markers Stable on 7 mg/kg			MKD complicated by AA amyloidosis; remained on therapy with prednisolone 0.5 mg/day	Stabilized on monotherapy	After starting hospital admissions dropped 11/year to 3/year Given in combination with IV methylprednisolone first 3 years then as monotherapy

IV intravenous; *NSAID* non-steroidal anti-inflammatory drug; *CR* complete response; *PR* partial response; *URI* upper respiratory infection; *AE* adverse events

ment is to reduce the production of the hepatic acute phase response protein SAA, which is the amyloid fibril protein [51]. IL-6 is a major stimulant of the hepatic acute phase response so its use in AA amyloidosis is rational. Responses have been generally encouraging and suggest that effective treatment results in improvement of clinical symptoms as well as biochemical inflammation.

Ugurlu et al., reported a series of 12 Turkish patients with FMF complicated by AA amyloidosis. Four patients had coexistent ankylosing spondylitis and one had Crohn disease. Tocilizumab was given in addition to colchicine and was well tolerated. Treatment resulted in a biochemical response in all cases with decreased proteinuria without loss of renal function during follow-up. Ten patients had no clinical FMF attacks on treatment, one had episodes of erysipelas like erythema and one reported an amelioration in the attack frequency [52]. Lane et al. reported a series of 14 patients with AA amyloidosis treated with tocilizumab, of whom one had MKD, one

unclassified systemic autoinflammatory disease and one with Castleman disease. The remaining cases included 7 patients with refractory rheumatoid arthritis and 4 with systemic juvenile idiopathic arthritis. Tocilizumab effectively reduced the acute phase response in all cases with symptomatic benefit and improved quality of life measures. The series included four patents with renal transplants and two on dialysis; even in these immune compromised patients' treatment was well tolerated. Adverse events included respiratory and urinary tract infections, post-transplant Epstein Barr virus viremia, transient neutropenia and abnormal liver function tests. No patients discontinued treatment permanently as a result of adverse effects. There was evidence of amyloid regression on imaging in nine cases and no patient had worsening disease. No patients progressed to renal failure and proteinuria improved in all assessable cases [49].

42.5 Janus Kinase (JAK) Inhibitors

- **Janus kinase (JAK) inhibitors are the first agents to show benefit in the interferonopathies, although as yet there are very few published data**
- **The major adverse effect concern at present is the risk of viral reactivation, especially herpes zoster**

The JAKs are cytoplasmic protein tyrosine kinases that play a critical role in cellular response to cytokines including type I cellular immune responses and type II, antibody mediated responses. A simplified summary of the role of the JAK-STAT pathway is that binding of a cytokine induces dimerization of its cognate receptor (Fig. 42.2). This activates JAK resulting in reversible phosphorylation of the receptor dimer. STAT binds to the phosphorylated receptor and in turn is phosphorylated by JAK. The resultant dimer of

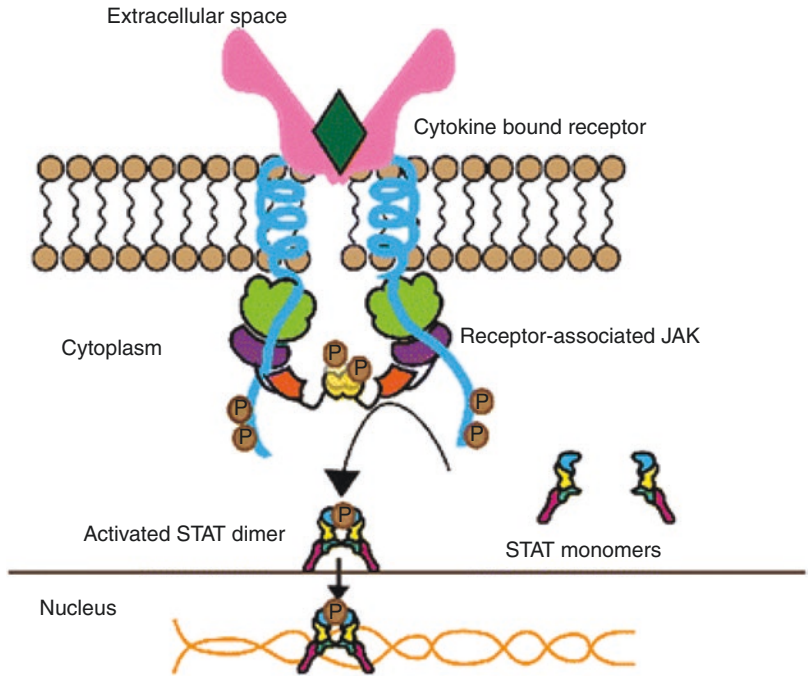

Fig. 42.2 Cytokine signalling through the Janus kinase (JAK)-signal transduction and activation of transcription (JAK/signal transducer and activator of transcription-STAT) pathway. Binding of a cytokine to the receptor leads to activation and phosphorylation of JAK and phosphorylation of the receptor. This in turn leads to phosphorylation and dimerization of STAT. Activated STAT dimer migrates to the nucleus and binds to specific DNA-binding sites regulating gene transcription. This culminates in alteration of cellular function. Reproduced with permission from Banerjee et al. Drugs 2017 [53]

phosphorylated STAT translocate to the nucleus thereby activating gene transcription [53]. Mutations in JAK-STAT pathways have been implicated in a variety of diseases including severe combined immunodeficiency, rheumatoid arthritis, systemic lupus erythematosus, Crohn disease and Behçet disease [54].

There are four JAKs: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). They are each associated with specific cytokine receptors and STATs (Table 42.5).

JAK inhibitors are conventional small molecule pharmaceuticals which are orally active. The currently labelled drugs are summarised in Table 42.6. Most of the safety data derive from tofacitinib studies and preliminary data suggest that although the agents have different selectivity for JAK types the side effect profile is broadly similar. All these agents carry a risk of inducing cytopenia, dyslipidemia and abnormal liver function tests. The major adverse events reported to date are infections. Bacterial infections including pneumonia, urinary tract infections and soft tissue infections occur at a rate broadly similar to that seen with use of biologics in rheumatoid arthritis. It seems likely this is the case for tuberculosis too. In contrast, use of JAK inhibitors has

Table 42.5 Janus kinases (JAKs) and signal transducers of activation (STATs) with associated cytokines

JAK	Major role in cytokine signalling	STAT
JAK1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-13, IL-15, INF-α/β, NF-γ, IL-21	STAT 1, 2, 3, 5, 6
JAK2	IL-3, IL-5, IL-6, IL-12, IL-13, IL-19, IL-23, GM-CSF, G-CSF, GH, erythropoietin, INF-γ	STAT 1, 3, 4, 5, 6
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	STAT 3, 5, 6
TYK2	IFNα/β, IFNγ, IL-6, IL-12, IL-23	STAT 1, 2, 3, 4, 6

TYK tyrosine kinase; *IL* interleukin; *INF* interferon; *NF* nuclear factor; *GM-CSF* granulocyte-macrophage colony-stimulating factor; *G-CSF* granulocyte colony-stimulating factor; *GH* growth hormone

Table 42.6 Comparison of currently labelled Janus kinase (JAK) inhibitors

	Tofacitinib	Baricitinib	Ruxolitinib
Major Target	JAK 1, JAK3, and JAK 2 to a lesser extent	JAK 1 and 2	JAK 1 and 2
Route of administration	Oral or topical	Oral or topical	Oral
Standard maintenance dose in adults	5–10 mg	4 mg	5–20 mg (depending on platelet count)
Dose frequency	Twice per day	Once per day	Twice per day
Labelled indications	Rheumatoid arthritis as monotherapy or combined with methotrexate	Rheumatoid arthritis as monotherapy or combined with methotrexate[a]	Disease related splenomegaly in myelofibrosis
Clinical trials	Psoriasis and psoriatic arthritis, ulcerative colitis, vitiligo, alopecia areata, systemic juvenile idiopathic arthritis	Psoriasis, diabetic nephropathy, systemic lupus erythematosus, atopic dermatitis	
Major adverse events	Abdominal pain/gastritis; nasopharyngitis; anemia; dyspnea/cough; diarrhea; dyslipidemia; headache; hypertension; insomnia; leukopenia; peripheral edema; pyrexia; raised liver enzymes; rash; vomiting; weight gain; infection (including serious bacterial, fungal, viral and mycobacterial infection); lymphopenia; neutropenia	Gastroenteritis; herpes simplex; herpes zoster; BK viremia; dyslipidemia; thrombocytosis; venous thrombosis; upper respiratory tract infection; urinary tract infection; acne; neutropenia; weight gain	Anemia; thrombocytopenia; neutropenia; bleeding and weight gain

[a]Approved for rheumatoid arthritis by the United States of America Food and Drug Administration at a 2 mg/day dose

a much higher risk of viral infections, particularly reactivation of herpes zoster. The risk in rheumatoid patients seems to be potentiated when taken together with corticosteroids and/or methotrexate [45]. To date there is no convincing evidence of an increased risk of malignancy but given the small number of exposed patients and relative short length of follow up subtle alteration in risk would not be expected to have become apparent as yet [54]. Inhibitors targeting JAK2 carry a risk of resistance to growth hormone, which is potentially clinically significant in children and perhaps venous thrombotic events (at higher doses). Certainly a postulated cause of short stature in chronic renal failure is impaired phosphorylation of JAK2/STAT5b after growth hormone stimulation [55].

42.5.1 Use of Janus Kinase (JAK) Inhibitors in Interferonopathies

Evidence of a chronically elevated IFN response gene signature in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) and STING-associated vasculopathy with onset in infancy (SAVI) patients suggested a pathologic role of increased IFN signalling. Although treatment is being used in individual patients very little data have been published. A compassionate use program in pediatric patients has been on-going at the USA National Institutes of Health since 2011. Preliminary results on 18 patients (10 with CANDLE, four with SAVI and four with presumed CANDLE-related conditions) treated with baricitinib for a mean 3.0 years were published in 2018 [56]. Half of the CANDLE patients were maintained in clinical remission and clinical features; inflammatory biomarkers and the interferon signature improved in patients with SAVI. Three patients discontinued treatment, two with genetically undefined disease for inefficacy and one with CANDLE for tubulointerstital nephritis and BK viremia. One patient developed herpes zoster. BK viremia developed in 44% of patients with low, stable viral titres on continued treatment. These patients did not develop clinical sequelae and remain under observation. In a pharmacodynamics paper the authors suggested dosing regimens dependent on weight and renal function, with the starting dose of 4 mg twice daily in patients with >40 kg weight and normal renal function. This dosing was sufficient to decrease STAT phosphorylation in four cell populations and reduce downstream markers of INF signalling, as assessed by a 25-gene panel [57].

42.6 Future Developments in Therapeutics

- **There is an unmet need for treatment in many rare systemic autoinflammatory diseases**
- **Even where effective treatments exist biologics are prohibitively expensive for many health care systems and require parenteral administration**

42.6.1 Inflammasone Inhibitors

The increasing evidence that activation of nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain 3 (NLRP3) may play a role in the pathogenesis of common acquired diseases such as type 2 diabetes, atherosclerosis, obesity, gout, neurodegenerative diseases, fibrotic pulmonary diseases, liver and kidney disease and malignancy (see Chap. 39) has fuelled interest in developing small molecules as cost effective inhibitors of the inflammasome. One such agent, MCC950, has been shown to be a potent selective NLRP3 inhibitor in mice models of CAPS. The compound not only prevented activation of IL-1β by caspase 1 but also prevented maturation of IL-18 and pyroptosis. The compound was not disastrously immunosuppressive as it did not block the major antimicrobial inflammasomes NLRC4 and NLRP1, nor IL-1β maturation mediated by serine proteases and caspase-8 [58].

42.6.2 Repurposing of Drugs for Use in Systemic Autoinflammatory Diseases

Rare diseases disproportionately affect the young, often the very young, and are associated with poor outcomes. Currently there are few available therapeutic options; in fact, more than 95% of rare diseases have no labelled treatments. Consequently, there is intense pressure to find effective, affordable treatments. Repurposing of drugs is an appealing approach which carries less commercial risk, saving time and money by focussing on agents which have already met regulatory requirements and undergone post-market monitoring. In the past identification of novel indications relied on clinical acumen and serendipity; the recognition of colchicine as prophylactic treatment in FMF is a beautiful example of this (see Chaps. 16 and 40). Advances in computing which enable data mining from the academic literature, regulatory documentation, clinical trials and electronic health records combined with research tools such as high through-put "signalome" screening allows for rapid identification of and screening of potential therapeutics. Work using these approaches in TRAPS has suggested fluoroquinolone antibiotics may downregulate disease specific signalling pathways [59]. Similarly squalene synthase inhibitors, previously developed for the treatment of hyperlipidemia, are now being explored in the treatment of MKD [60].

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