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HANDBOOK

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# Autoimmune disease: Focus on management

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# Foreword

In the second educational handbook of this series centring on key immune-mediated diseases (IMIDs), we move from the fundamentals and focus on management of disease this time. Here, we consider the underlying pathophysiology, diagnosis, clinical guidelines and the potential supportive role of pharmacists for those with an IMID.

While differences exist in the organ system affected and thus clinical presentation of IMIDs, a common feature may be the existence of a genetic predisposition. In the presence of potential triggers among those with this genetic susceptibility, the ensuing immune response and cytokine milieu initiates a series of reactions. These reactions culminate in the symptomatic profile of the IMID.

With an improved understanding of the pathophysiological events underpinning the development of an IMID comes the recognition that specific biomarkers can be used diagnostically for the different diseases. Consequently, both laboratory testing and histological findings are crucial and supplementary components for diagnosis rightly deserve a dedicated chapter in this handbook. Furthermore, the identification of biomarkers in combination with clinical symptoms has led to the development of management guidelines for these conditions. To date, several European and international groups have produced best practice guidance on IMIDs, and which are also discussed in this handbook. Given a population prevalence of 0.5–1%, the handbook also provides a comprehensive chapter dedicated to the management of rheumatoid arthritis.

With a greater understanding of the pathology of IMIDs comes the recognition of specific molecular targets that are the site of action for biologic drugs. While only introduced to clinical practice during the 1980s, biologics have revolutionised the treatment of a number of conditions across the clinical spectrum and IMIDs are no exception. But as biologics are derived from living systems, treatment is expensive. Consequently, the use of biologics has exerted great financial pressure on healthcare systems across the globe. Nevertheless, more recently, the introduction of biosimilars, which are clinically equivalent to biologics and are more-cost-effective, has enabled the wider access to treatment for those with more severe immune-mediated disease. Although the financial benefits of biosimilars are clear, the wider adoption of these cost-effective alternatives has been stifled to some extent due to a number of barriers. Despite these, biosimilars are set to play a pivotal role in the management of patients with more severe IMID and a chapter in this handbook is devoted to these important therapeutic developments.

Finally, as with most therapeutic interventions, it is important not to neglect the role of patient education. Non-adherence to treatment is a recognised cause of

therapeutic failure. While there are several interacting and contributory factors leading to non-adherence, patients' understanding of both their disease and the therapeutic objectives is crucial. Such knowledge expedites a more active role in disease management, empowering patients to become more involved in treatment-related decision-making. As the experts in medicines, pharmacists have a vital role to play in supporting patients with IMIDs. Through education, pharmacists can enhance patients' understanding of not only their conditions but also the medicines used to treat the condition, alerting them to any potential side-effects and the importance of adherence. In fact, the available evidence clearly illustrates how pharmacist-led education improves both adherence and clinical outcomes for patients with rheumatoid arthritis. Furthermore, other evidence reveals how pharmacists have a pivotal role in medication reviews for those already established on treatment for an IMID.

This second and complementary handbook offers the reader a further and impactful resource on IMIDs, from their underlying pathophysiology to therapeutic management. Equally, it offers a valuable insight as to the potential role of pharmacists in supporting patients to ensure that they achieve the best possible outcomes for condition.

# Pathogenesis of immune-mediated inflammatory diseases

Here we focus on commonalities and differences in the pathogenesis of the main immune-mediated diseases in rheumatology, dermatology and gastroenterology

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Immune-mediated inflammatory diseases (IMIDs) are a heterogeneous group of conditions characterised by chronic inflammation and organ damage. This definition includes a diverse group of chronic inflammatory diseases in which the innate and/or adaptive immune system plays a predominant role in their pathogenesis. They range from autoinflammatory to autoimmune in nature, with many of them exhibiting a mixed disease pattern.[1]

The clinical spectrum of these diseases includes joint inflammation (rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (ax-SpA)), gut inflammation (Crohn's disease (CD), ulcerative colitis (UC)) and skin inflammation (psoriasis (PsO), PsA). Globally, they affect around 5% of population, predominantly young and middle-aged people, and they share: a chronic progressive clinical course with target tissue infiltration by immune-inflammatory cells and organ damage; and genetic variants associated to increased susceptibility, cytokine pathways and therapeutic targets. However, there are also specific differences between them. The knowledge of pathogenetic mechanisms shared by these diseases has been derived from randomised clinical trials (RCTs) resulting in the approval of targeted biologics. Schett and McInnes have proposed that these commonalities could justify a multidisciplinary approach to molecular pathogenesis instead of the classic organ-based approach.[2]

## Pathogenesis of IMIDs

In general, patients with IMIDs have a genetic predisposition, and triggers such as infections, obesity or biomechanical factors can activate dendritic cells (DCs), macrophages, and other antigen-presenting cells (APCs) to present antigens through the MHC class I or II to Tcd8+ and Tcd4+ cells, respectively. This process triggers innate and adaptive immune responses by promoting the local release of cytokines.
The type of antigen presented, and the type of stimulating cytokines present in close proximity, determines the pattern of immune response and effector cytokine secretion. T helper (Th) 0 cells can differentiate into effector Th1, Th2, Th17, or regulatory T (Treg) cells. The presence of interleukin (IL)-12 and interferon (IFN)-α stimulates the Th1 response, leading to the release of tumour necrosis factor (TNF)-α and IFN-γ. IL-4 stimulates Th2 response: releasing IL-4, IL-5, and IL-13, which are considered to have anti-inflammatory or protective functions. IL-23, transforming growth factor (TGF)-β, IL-6, and IL-1b activate the Th17 response, leading to the release of IL-17, IL-22, IL-26, and CCL20. Additionally, the presence of IL-2 and TGF-β stimulates the development of Treg cells, secreting IL-10 and TGF-β, which deactivate the inflammatory cascade. Treg cells also play a role in maintaining tolerance to self-antigens. Furthermore, most of the genetic variants associated with IMIDs discussed here result in strong activation of the innate immune system due to an abnormal response to DAMPS (damage-associated molecular patterns) and PAMPS (pathogen-associated molecular pattern).

The different types of cytokines secreted interact with their transmembrane receptors, promoting the release of more cytokines and chemokines attracting and/or activating stromal, lympho-myeloid and epithelial cells, such as endothelial cells, fibroblasts, monocyte-macrophages, dendritic cells (DC), keratinocytes, epithelial cells, chondrocytes, osteoclasts and osteoblasts. Activation of the immune system leads to systemic inflammation, synovitis, enthesitis, bone remodelling (erosions, bone proliferation), intestinal mucosal erosions and keratinocyte hyperplasia of the skin[3–7]

## T cells in IMIDs

The T-cell response is restricted by the HLA molecule (expressed in the membrane of the antigen-presenting cell) containing the antigen. HLA-class I presents antigens to Tcd8+ cells, whereas HLA-class II molecules present antigens to Tcd4+ cells. Theoretically, IMIDs associated to HLA class I alleles induce a TCd8+ response, whereas those associated to HLA class II alleles induce a TCd4+ response. In fact, in PsA, ax-SpA and PsO the main effector response is driven by IL-17+Tcd8 cells, but IL-17+CD4+ also are abundant in joints and skin; Th1/Th17 cells, a dynamic transition cellular state expressing IFN+ (Th1) and IL-17+ (Th17), also have a role in the pathogenesis of those IMIDs. Regarding RA, which is induced by a breach of immune tolerance involving T-, B- and DC, CD4+T cells (peripheral and follicular T cells), B cells and dendritic cells are predominant in the synovial membrane, leading to plasma cell differentiation and autoantibody production as well as to activation of synovial fibroblasts with IL-6 release. In CD, IL-23 secreted by DC and macrophages in the ileal and colonic wall produces TCD4+ cells (Th1 and Th17), whereas in UC, Th2 cells are increased and induce eosinophil infiltration through IL-13.[2] (see Table 1).

## Genetic factors of IMIDs

The development of IMIDs can be influenced by variations in multiple genes (alleles). Most of those genes are localised in the major histocompatibility complex (MHC), a large region →

**TABLE 1**

## Genetic associations, immunopathological landmarks and approved cytokine signature therapies in IMIDs

| Variable | RA | PsA | ax-SpA | PsO | CD | UC |
|---|---|---|---|---|---|---|
| **Main genetic associations** | HLA-DR4<br>PTPN22<br>CTLA4 | HLA-B27<br>IL-23R,<br>IL-12RB, A20<br>HLA-C06 | HLA-B27<br>IL-23R<br>ERAP-1 | HLA-C06<br>IL-23R<br>IL-12RB | HLA-DRB1<br>IL-23R<br>NOD2 | HLA-DRB1<br>IL-23R<br>IL-10 |
| **Drivers** | Autoimmunity | Mechanical stress and metabolism | Mechanical stress | Physical injury<br>Infection<br>Medication | Microbial dysbiosis and barrier dysfunction | Microbial dysbiosis and barrier dysfunction |
| **Key pathological process** | Synovitis | Enthesitis and synovitis | Axial enthesitis | Keratinocyte hyperplasia | Granuloma formation | Cryptitis |
| **Cellular immune response** | B cells, T cells, Macrophages, Fibroblasts | Th17 cells,<br>Tg/d cells<br>ILC3<br>Neutrophils,<br>Fibroblasts | Th17 cells,<br>Tg/d cells<br>ILC3<br>Neutrophils | Keratinocytes<br>Dendritic cells<br>Th1, Th17,<br>Th22 cells<br>Neutrophils | Th1/Th17 cells<br>Dendritic cells<br>Macrophages | Th1/Th9/<br>Th17 cells,<br>Neutrophils |
| **Approved TNF-alpha inhibitors** | Adalimumab<br>Etanercept<br>Certolizumab<br>Golimumab<br>Infliximab | Adalimumab<br>Etanercept<br>Certolizumab<br>Golimumab<br>Infliximab | Adalimumab<br>Etanercept<br>Certolizumab<br>Golimumab<br>Infliximab | Adalimumab<br>Etanercept<br>Certolizumab<br>Golimumab<br>Infliximab | Adalimumab<br>Certolizumab (US)<br>Infliximab | Adalimumab<br>Certolizumab (US)<br>Golimumab<br>Infliximab |
| **Approved cytokine signature drug (targets)** | Tocilizumab (IL-6Ri)<br>Sarilumab (IL-6Ri) | IL17Ai:<br>Secukinumab<br>Ixekizumab<br>IL12/23i:<br>Ustekinumab<br>IL23p19i<br>Guselkumab<br>Risankizumab | IL17Ai:<br>Secukinumab<br>Ixekizumab | IL17Ai:<br>Secukinumab<br>Ixekizumab<br>IL12/23i:<br>Ustekinumab<br>IL23p19i<br>Guselkumab<br>Risankizumab | IL-12/IL-23i<br>Ustekinumab | IL-12/IL-23i<br>Ustekinumab |

Modified from ref 2.
Abbreviations: **IMIDs**: immuno-mediated inflammatory diseases: **HLA**: Human leukocyte antigen; **IL**:interleukin; **IL-23R**: IL-23 receptor; **IL-12BR**: IL-12beta receptor; **A20**: TNFAIP3; **Th**: T helper; **Tg/d**: gamma/delta T cells; **ILC3**: innate lymphocyte type 3; **IL17i**: IL-17 inhibitors; **IL-6Ri**; IL-6 receptor inhibitor

on the short arm of chromosome 6, which houses a multitude of polymorphic genes with immunological functions, including those related to antigen presentation (human leucocyte antigen; HLA). Several HLA-class I alleles have been associated with PsO (HLA-C*06:02), axSpA (HLA-B27) and PsA (HLA-B27, HLA-C06).[8] Furthermore, certain combination of alleles (haplotypes) has been associated with distinctive clinical phenotypes in PsA: HLA-B08:01-C07:01 has been linked to asymmetric sacroiliitis, while HLA-B27:05-C01:02 and B27:05:02-C02:02:01 were associated to symmetric sacroiliitis, dactylitis and enthesitis. By contrast, distinct HLA-class II alleles have been associated with anti-citrullinated protein antibody (ACPA)+ve RA (HLA-DR4, -DR1), ACPA-ve RA (HLA-DR3), CD (HLA-DRB1) and UC (HLA-DRB1).[9–11]

Genome-wide association studies (GWAS) have enabled the identification of multiple susceptibility genes and loci associated with IMIDs. ACPA+ve RA is associated with genetic variants (single nucleotide polymorphisms, SNP) of protein tyrosine phosphatase non-receptor type 22 (PTPN22), which lower the activation threshold of T-cells, and with CTL4 variants, which codes for a co-stimulatory molecule relevant to T activation.[12]

Importantly, GWAS have identified several variants in genes of the IL-23/IL-17 axis which defines an immuno-inflammatory pathway of cytokines characteristic of IMIDs with skin, joint or bowel inflammation. Single nucleotide polymorphism variants at the IL-23 receptor gene (IL-23R) are associated with PsO, PsA, CD and UC, but do not always have the same effect; for example, the variant IL-23R-Arg381Gln confers a protective effect on IBD. Variants at the IL-23R and IL-12RB genes have an independent association with PsA and PsO.[13,14]

TNFAIP3 (A20) and TNIP1 genes code for proteins that interfere with the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) pathway, resulting in negative regulation of inflammatory signaling. Variants of these genes lead to loss of function and are linked to susceptibility to PsA.[15]

Finally, variants of nucleotide-binding oligomerization domain 2 (NOD2), an autoinflammatory gene member of the

cytosolic Nod-like receptor (NLR) family, that senses microbial invaders and leads to the secretion of proinflammatory cytokines and activation of the MAPK signaling pathway, are associated to development of CD.[16]

### Cytokine pathways and therapeutic targets in IMIDs

RCTs, together with significant experience on their administration in clinical practice, have demonstrated that these IMIDs respond well to TNF-α inhibition (TNFi). This confirms the key role played by this cytokine in their pathogeneses, by inducing secretion of other proinflammatory cytokines (IL-1, IL-6, GM-CSF) by TNF-activated monocyte-macrophages, T cells and synovial fibroblasts. Of note, in contrast to RA, the other IMIDs discussed here also share the IL-23/IL-17 cytokine axis pathway, with some interesting differences between them. PsO and PsA show good responses to IL-23 and IL-17 inhibitors, but with much stronger responses in skin than in joints, whereas ax-SpA responds to IL-17 inhibitors, but not to IL-23 inhibitors. CD and UC respond well to IL12/IL-23 and IL-23 inhibitors, but not to IL-17 inhibition, which highlights the different role that these cytokines play in the different affected tissues. In short, each involved tissue determines the immune response at the local level.[2]

Surprisingly, even though CD is associated with variants of an autoinflammatory gene (NO2) and driven by Th1 and Th17 cells, and UC is linked to variants of IL-10R and driven by Th2 and Th9 lymphocytes and innate lymphoid cells type 2 (ILC2), both diseases share TNF and IL-23 as therapeutic targets.

The cytokine hub in RA is based in TNF and IL-6. IL-6R inhibition is not effective in PsA, axSpA or IBD.

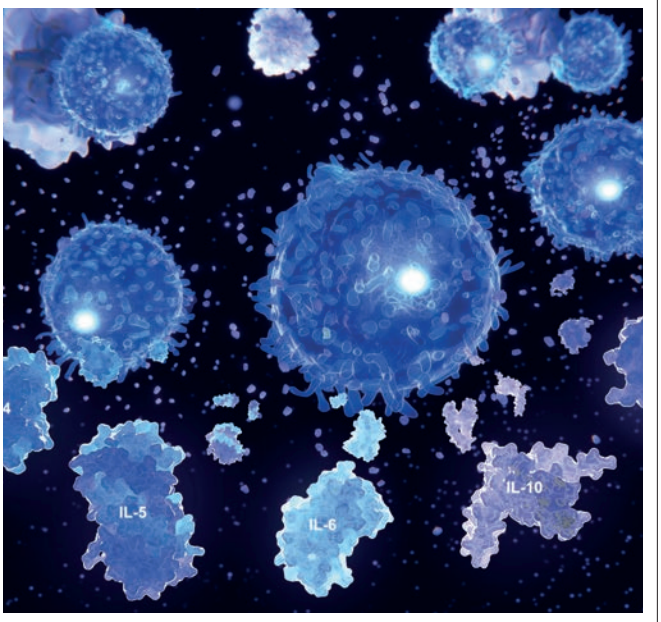
### Intracellular signaling pathways

Transmembrane receptors, including STAT3 and Janus kinase 2 (JAK2), are also implicated in IMIDs. The JAK-STAT pathway plays a pivotal role in transmitting signals downstream of cytokines and growth factors from cell-surface receptors to the nucleus to modify the transcription of multiple genes. JAK2 is involved in IL23R signalling and STAT3 plays a central role in Th17 differentiation.[17] In addition, JAK2 or STAT3 are also downstream of several other cytokines implicated in the pathogenesis of IBD, PsO and PsA, highlighting the pathophysiologic complexity of these associations.[18] STAT4 has a modest association with RA, but plays a crucial role in IL-12 signaling in T and natural killer cells, which leads to IFN-γ production and differentiation of CD4 T cells into a Th1 phenotype.[19,20] Upon binding to the IL-12R, STAT4 is phosphorylated and forms homodimers, which are then translocated to the nucleus to initiate transcription of STAT4 target genes, including IFN-γ.[21]

### Conclusion

The advent of biologics targeting specific cytokines has revealed key information on the pathophysiology of IMIDs affecting skin, joints and gut. This knowledge paves the way for a mechanism-based understanding of IMIDs. At the same time this highlights the relevance of tissue determinants in shaping the local function of cytokines. Detailed analysis of cytokine hubs by means of Omics technologies could identify molecular pathotypes within a clinically defined disease, improving the stratification of patients according to their cytokine pathways. For example, by sharing a similar immunopathologic pathway, an IL-23-driven CD pathotype may be more similar to an IL-23-driven PsA pathotype than to a distinct pathotype of CD.

These insights into the genetic and immunopathologic pathways shared by PsO, PsA, ax-SpA, CD, UC and RA are a key step towards the definition of disease-associated signature cytokine hub which will improve targeted intervention for these IMIDs.[2]

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# Diagnosis of immune-mediated diseases: What role for laboratory tests?

Laboratory testing is of great value when evaluating suspected immune-mediated diseases. Tests can confirm a diagnosis, estimate disease severity, and help assess prognosis and disease progression
Comprehensive evaluation of a suspected IMID in conjunction with in-depth clinical assessment provides a sound understanding of these conditions

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The vast landscape of immune-mediated diseases (IMIDs), together with their clinical heterogeneity, make diagnosis one of the most challenging tasks in the clinician's routine. These diseases can manifest with similar symptoms and signs, such as joint pain or rash, which can, in turn, be associated with very different clinical outcomes. Also, severe, life-threatening manifestations are seldom observed, their probability depending on the underlying diagnosis. For example, lupus and vasculitis can severely impair the kidney, whereas psoriatic arthritis can be associated with inflammatory bowel disease or ocular inflammation.

The therapeutic approaches are very different, so achieving the correct diagnosis is of paramount importance.

### Initial laboratory testing – the backbone of diagnosis

There is no one test that can accurately diagnose a particular IMID. First-line laboratory tests, often inaccurately referred to as 'routine', include complete blood cell count, acute phase reactants (mainly C-reactive protein), serum creatinine, liver function tests, and serum protein electrophoresis.

Table 1 shows some of the common tests used for IMIDs.

### Blood count

White blood cells play an important role in inflammation, and lymphocytes orchestrate the adaptive immune response. Rheumatic diseases affect white blood cell count and increased numbers (leukocytosis) are a factor in inflammatory states. Evaluation of single leukocyte populations is also of great importance, because an increased neutrophil count might suggest inter-current infection, whereas neutropenia or lymphopenia (i.e. decreased number of white blood cells) are more often seen in lupus flares, or as consequence of immunosuppressive therapies.[1] Blood cell counts can reveal anaemia, which is a typical sign of chronic inflammation. Anaemia can result from causes unrelated to inflammation, such as chronic blood loss, vitamin deficiencies, or red blood cell destruction (i.e., haemolysis) that can be related to autoimmune disorders. Increased platelet count is another biomarker of severe inflammation and is observed in vasculitis, whereas systemic lupus erythematosus can lead to thrombocytopenia.[2,3]

**TABLE 1**

**Common tests for IMIDs**

- C-reactive protein
- Erythrocyte sedimentation rate
- Complete blood count
- Coagulation studies (activated partial thromboplastin time/ prothrombin time)
- Liver function tests
- Urea and electrolyte panel
- Vitamin B-12/D
- Ferritin/transferrin tests
- Autoantibodies

### Acute phase reactants

Acute phase reactants are proteins released during the inflammatory response, and their levels can be measured in serum.

C-reactive protein (CRP) is the primary inflammatory biomarker and is synthesised by the liver following stimulation by inflammatory cytokines. CRP is teleologically aimed at recognising circulating pathogens and damaged tissues.[4] Inflammation skews the hepatic synthesis of plasma proteins, by decreasing the levels of albumin (which is normally the most abundant plasma protein) and increasing the levels of alpha-1-globulins. Such changes, together with the increase in immunoglobulins secondary to lymphocyte activation, are reflected by changes in serum electrophoresis.[4]

Fibrinogen, the soluble precursor of fibrin required for blood clot formation, is another acute phase reactant and elevation is often seen in rheumatic diseases, especially in cases of suspected vasculitis.

### Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR), the longest-established inflammatory biomarker, is the rate (expressed in mm/hour) that a suspension of red blood cells precipitates when placed in a vertical tube. The rate correlates with plasma fibrinogen concentration. Despite being often neglected, ESR is very important in certain conditions, such as systemic lupus erythematosus, where elevated ESR should raise suspicion of disease flare in the presence of normal CRP levels (whereas elevation of both ESR and CRP is suggestive of inter-current infection).[5]


**Complement**
The complement cascade is a set of serum proteins that destroys microbes and damaged cells. Certain IMIDs can improperly activate the complement cascade, thus decreasing the levels of circulating fractions (C3 and C4). Low levels of serum complement fractions support the diagnosis of a lupus flare in the appropriate clinical context.

**Ferritin**
Among acute phase proteins ferritin, a protein residing in the cell cytoplasm, is increased during inflammation, and hyperferritinaemia is observed in severe inflammatory syndromes (e.g., macrophage activation syndrome, cytokine storm). Hyperferritinaemia is also a predictor of severe COVID-19 pneumonia with deleterious systemic consequences.[6]

**Serum creatinine**
Some IMIDs can severely impair renal function and this is assessed by measuring serum creatinine at diagnosis and periodically during follow-up.

Routine chemistry tests are powerful diagnostic tools to evaluate inflammation and organ involvement in cases of suspected IMIDs; however, the tests are neither sensitive nor specific enough to be considered 'diagnostic' in an absolute way.

## Serum autoantibodies – the path of diagnosis

Autoantibodies (antibodies directed towards components of cells and tissues) are the hallmark of several autoimmune diseases, and their presence is significant in both diagnosis and prognosis. Autoantibodies are associated with specific conditions, but their presence is neither definitive nor mutually exclusive. For example, antinuclear antibodies (ANA) are almost always present in patients with systemic lupus erythematosus,[7] but can be observed in up to 20% cases of rheumatoid arthritis, as well as following viral infections (e.g., hepatitis C and COVID-19). Autoantibodies can be also detected in healthy subjects without signs of autoimmunity.[8] Thus, serum autoantibody testing should not be intended as a screening tool but ordered only if there is clinical suspicion of autoimmune disease.[9]

**Rheumatoid factors**
Rheumatoid factors are autoantibodies present in rheumatoid arthritis. Tests have good sensitivity but limited specificity, meaning there is the potential for false positives. Rheumatoid factors can be also observed following chronic infections and in cryoglobulinaemic syndrome, an inflammatory vasculitis associated to hepatitis C and presenting with typical skin lesions, kidney, and nerve involvement. Detection of rheumatoid factors relies on solid phase assays.[10]

**Anti-citrullinated protein antibodies (ACPA)**
ACPA can also be observed in patients with rheumatoid arthritis, displaying excellent specificity. These antibodies are directed towards modified proteins involved in disease pathogenesis: theories postulated to explain such modifications include smoking, periodontal disease and chronic respiratory infections but the disease aetiology remains unknown.[10]

**Antinuclear antibodies (ANA)**
Autoantibodies to nuclear antigens are a diverse group that react to cellular antigens such as nucleic acids, histones, nuclear and ribonuclear proteins. ANA hallmarks the detection of systemic lupus erythematosus, although ANA are common in other autoimmune diseases. ANA testing thus requires careful interpretation. ANA are detected in up to 10% of the healthy population.[8] Indirect immunofluorescence on the HEp-2 cellular line (HEp-2 IFA) is the reference standard for ANA detection, and provides the following information:
**1** the presence of ANA in the tested serum;
**2** the titre, that is, a surrogate of autoantibody concentration/quantity;
**3** the pattern, that is, how autoantibodies arrange themselves in the staining, and which reflects the cellular structures and possible antigen specificities.[11]

Whereas the titre generally correlates with the probability of a true positive test, the pattern differs depending on the specificity; that is, the antigen towards which the autoantibody is directed. A positive ANA test should always be confirmed with solid-phase assays to confirm specific antigens, often referred as the extractable nuclear antigens (ENA) SSA/Ro, →

SSB/La, RNP, Scl-70, and Sm.[9] Once again, physicians should test for ANA and specific antibodies only when there is relevant clinical suspicion.

### Antineutrophil cytoplasm antibodies

There is a rare subset of serum autoantibodies directed towards antigens located in the cytoplasm of neutrophils; namely the antineutrophil cytoplasm antibodies (ANCA). ANCA-associated vasculitides include Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis.

Indirect immunofluorescence was the traditional method for serum ANCA detection, leading to two possible staining patterns: cytoplasmic or c-ANCA; and perinuclear or p-ANCA. It was then discovered that c-ANCA are mainly directed towards the neutrophilic enzyme proteinase 3 (PR3) and associated to Wegener's granulomatosis, whereas p-ANCA recognise myeloperoxidase (MPO) and are found in microscopic polyangiitis and in some patients with Churg-Strauss syndrome. pANCA have now been observed in a variety of diseases including other types of vasculitis, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, and juvenile idiopathic arthritis.

Solid-phase assays for PR3 and MPO display higher sensitivity and specificity than immunofluorescence and are therefore the reference standard for ANCA detection in cases of suspected associated vasculitis.[12]

### Genetics and cytokine studies

IMIDs can be associated with polymorphisms in the human leukocyte antigen (HLA) system, an ensemble of proteins that is required for lymphocyte activation; it is thought that some polymorphisms correlate with an increased risk of developing autoimmune diseases. Spondyloarthritis is particularly associated to HLA-B27;[13] the presence of this gene can thus support the diagnosis in certain contexts. Similarly, HLA-B51 can support the diagnosis of Behçet's syndrome, a rare autoinflammatory vasculitis, in case of suggestive clinical features.[14] It must be highlighted that, whereas a significant proportion of patients with spondyloarthritis or Behçet's has HLA-B27 or B51, these antigens cannot be used as a screening test in the general population.

Cytokine studies are not routinely performed for the diagnosis of IMIDs. Since the COVID-19 pandemic, however, it has become more common to test for serum interleukin-6 (IL-6), with high levels being associated to more severe pneumonia and high risk of systemic inflammatory consequences closely resembling autoimmune phenomena.[15,16] IL-6 dosage, however, remains experimental in rheumatology. Idiopathic multicentric Castleman's disease is an extremely rare condition, that is often masked under an autoimmune-like clinical presentation. Despite poor specificity, serum levels of vascular endothelial growth factor can raise suspicion for Castleman's disease.[17] However, cytokine studies are not routinely performed to diagnose IMIDs.

### Histology

IMIDs are heterogenous, and depending on the clinician's needs, biopsies can be performed in a wide range of organs and tissues. The skin is often the most accessible site involved in diseases such as lupus, dermatomyositis, and vasculitis. In cases of suspected lupus, skin biopsy with direct immunofluorescence (the so-called 'lupus band test') can support the diagnosis, by detecting the deposition of antibodies and complement fractions at the epidermal basement membrane. Skin histology is also helpful in vasculitis, because the caliber of involved vessels and the presence of typical lesions (e.g., leukocytoclasia, fibrinoid necrosis, granulomas) can guide the diagnosis.[18,19] Similarly, muscle biopsy is important in differentiating inflammatory myositis from other forms of myopathy (including rare genetic forms as Duchenne's dystrophy).

Sjogren's syndrome is an IMID affecting the exocrine glands, especially the salivary and lacrimal glands. Biopsy of the labial minor salivary glands is important in its diagnosis, and histology can predict the risk of lymphoma, which is the most feared complication.[20] Finally, colonoscopy with intestinal biopsies can help revealing subclinical inflammatory bowel disease in a specific subset of patients with spondyloarthritis,[21] and this can help in selecting correct and personalised therapy.

### Conclusion

Accurate diagnosis is of critical importance for IMIDs. Mimics of autoimmune diseases, which are represented by infections (such as tuberculosis, endocarditis, hepatitis B and C, HIV, etc.) and malignancies need to be excluded; and microbiological tests, imaging, and histopathology findings are essential tools for this purpose. It is often challenging to distinguish between IMIDs because clinical similarities (i.e., same symptoms), and early and undifferentiated disease pictures often lead to diagnostic conundrums. Laboratory tests can help in differentiating conditions that require distinct therapies and dedicated follow-up. Laboratory medicine and pathology are thus of paramount and increasing importance for clinicians in appropriately managing patients with suspected and confirmed diagnoses of IMIDs.


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# Spotlight: Treatment guidelines

Here we shine a spotlight on some of the recent EU/UK treatment guidelines in dermatological, rheumatological and gastrointestinal immune-mediated diseases, navigating the main medical treatment options through a series of tables for easy reference

**TABLE 1**

## Dermatological conditions

| Condition | Medical management summary | | Key guidelines references |
|---|---|---|---|
| **Hidradenitis suppurativa** | • Analgesics for pain<br>• Keratolytic agents and antiseptics<br>• Topical/oral antibiotics/dapsone<br>• Retinoids | • Biologics (adalimumab)<br>• Immunosuppressive agents<br>• Intralesional corticosteroids<br>• Hormonal agents | 1–4 |
| **Psoriasis** | **Topical (mainstay for mild disease)**<br>• Topical corticosteroids<br>Vitamin D analogues<br>• Calcineurin inhibitors<br>• Keratolytics<br>**Oral therapy**<br>• Retinoids (e.g., acitretin)<br>• Immunosuppressants (e.g., ciclosporin, methotrexate)<br>• Fumaric acid esters<br>**Injectables (moderate to severe disease)**<br>• Various biologics targeting | different cytokine pathways e.g., IL-17, IL-12/23<br>• Anti-TNFα: infliximab, etanercept, adalimumab, certolizumab<br>• Anti-IL12/23: ustekinumab<br>• Anti-IL17: secukinumab, ixekizumab, brodalumab, bimekizumab<br>• Anti-IL23: guselkumab, risankizumab, tildrakizumab<br>• Anti-IL-36: spesolimab (the only one approved for generalised pustular psoriasis) | 5,6 |
| **Atopic dermatitis** | **Topical therapy**<br>• Emollients for all patients<br>• Topical steroids for disease flares<br>• Topical calcineurin inhibitors for sensitive areas e.g., face | **Systemic agents**<br>• Immunosuppressants<br>• Janus kinase (JAK) inhibitors<br>• Biologics (anti-IL-4/13: dupilumab; anti IL-13: tralokinumab) | 7–9 |
| **Vitiligo** | **Topical**<br>• Corticosteroids<br>• Calcineurin inhibitors | **Systemic**<br>• Oral corticosteroids (dexamethasone) | 10,11 |
| **Androgenic alopecia** | **Topical**<br>• Minoxidil<br>Corticosteroids (topical and intralesional)<br>• Calcineurin inhibitors, prostaglandin analogues, anthralin | **Systemic**<br>• Corticosteroids<br>• Alpha-reductase inhibitors | 12,13 |
| **Bullous pemphigoid** | **Topical**<br>• High potency corticosteroids | **Systemic**<br>• Oral prednisolone | 14 |
| **Pemphigus** | **Topical**<br>• Dapsone<br>• Topical corticosteroids | **Systemic**<br>• Corticosteroids<br>• Corticosteroids with immunosuppressants<br>• Rituximab | 15 |

**TABLE 2**

## Rheumatological diseases

| Condition | Medical management summary | Key guidelines references |
|---|---|---|
| **Psoriatic arthritis** | • Disease-modifying anti-rheumatic drugs (DMARDs)<br>• JAK inhibitors<br>• Biologics | 16,17 |
| **Axial spondyloarthritis** | • Biologics | 18 |
| **Giant cell arteritis** | • High dose glucocorticoids | 19,20 |
| **Systemic lupus erythematosus** | • Hydroxychloroquine<br>• Glucocorticoids | 21,22 |
| **Juvenile idiopathic arthritis** | • High dose glucocorticoids (for disease control)<br>• DMARDs<br>• Biologics | 23 |
| **Systemic sclerosis** | • Immunosuppressants<br>• Vasodilators (for Raynaud's manifestations)<br>• Proton pump inhibitors for gastric manifestations | 24,25 |
| **Vasculitis** | • High dose glucocorticoids<br>• Biologics (tocilizumab) | 26 |
| **Sjogren's syndrome** | • Topical ophthalmic and oral therapies for dry eyes/oral mucosa | 27,28 |
| **ANCA vasculitis** | • High dose glucocorticoids<br>• Rituximab<br>• Cyclophosphamide | 29–31 |

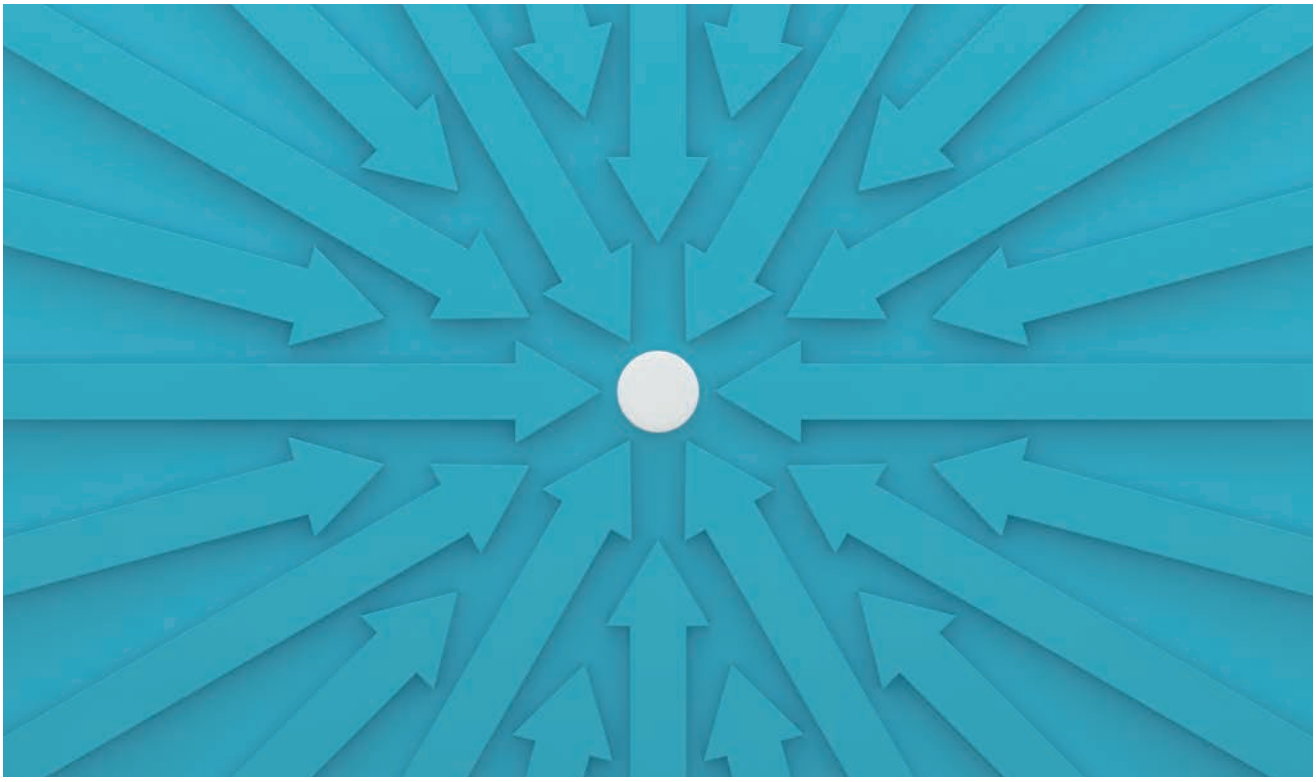
**TABLE 3**

## Gastrointestinal conditions

| Condition | Medical management summary | Key guidelines references |
|---|---|---|
| **Inflammatory bowel disease** | • 5-aminosalicylates (remission and maintenance)<br>• Oral corticosteroids<br>• Biologics | 32 |
| **Crohn's disease** | • 5-aminosalicylates (remission and maintenance)<br>• Oral corticosteroids<br>• Biologics | 33 |
| **Coeliac disease** | • Largely dietary management<br>• Immunosuppressants and oral glucocorticoids may help in refractory disease | 34,35 |
| **Ulcerative colitis** | • 5-aminosalicylates (remission and maintenance)<br>• Topical (rectal) corticosteroids<br>• Oral corticosteroids<br>• Biologics | 36 |

**Conclusion**

Clinical guidelines are a major part of the evidence-based toolkit for the clinician and healthcare professionals and play a fundamental role in improving the quality and process of care and optimising patient outcomes. They help healthcare professionals to navigate the complexities of treating these diverse groups of diseases and facilitate informed decision-making between patient and clinician. →

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# Current treatment options and standard of care: Focus on rheumatoid arthritis

Here we focus on rheumatoid arthritis and detail how early intervention, the advent of highly efficacious targeted therapies and a treat-to-target approach to management has dramatically improved the outlook for people presenting with this condition over the last generation

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Rheumatoid arthritis (RA) is a systemic inflammatory syndrome with autoimmune features having a predominant expression in peripheral synovial joints. It is the most common form of inflammatory polyarthritis with a population prevalence of between 0.5% and 1%. Once established and, if persistently active, RA generally becomes straightforward to recognise and is characterised by a deforming symmetrical polyarthritis, although the extent and severity differ widely. However, the variability of the presentation in the early stages of the illness is such that diagnosis, or classification, can be very difficult.[1] Rapid referral to a secondary care specialist is indicated when features of persistent inflammatory arthritis are suspected. This allows the diagnosis to be established and very early initiation of conventional synthetic disease modifying anti-rheumatic drug (csDMARD) treatment, before the onset of erosions, greatly reduces the risk of future joint damage and disability. Delayed treatment initiation and late achievement of remission or low disease activity are major predictors of poor long term clinical, functional and radiographic outcomes. A delay in referral is one of the most important causes of late diagnosis and a corresponding delay in initiating effective treatment.

## Treatment goals

The primary goal of treating patients with RA is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and participation in social and work-related activities. The most effective way to achieve this goal is by means of 'treat-to-target' strategies designed to intensively suppress synovitis. Recommended practice is to treat to a target of remission or low disease activity, as assessed by composite scores of disease activity, and to titrate therapy according to response.[2] The principle aims of a tight control approach as originally conceived were to limit or prevent the potentially devastating impact of structural damage in RA and preserve functional status. Although these aims remain an imperative of RA management, the problem of progressive structural damage to joints has become less marked in contemporary times than it was in past RA populations.[3] Consequently, while prevention of deformity and functional loss remain key long-term treatment goals, as are prevention or limitation of comorbidities and mortality, the nature of unmet need is shifting away from being predominated by inexorably progressive joint destruction. Many symptoms most troublesome to those living with RA are subjective in nature and their true impact is known only to the patient themselves,[4] including pain, fatigue, and mental function, all of which can adversely affect social interactions, employment, sexual activity, and overall wellbeing.[5]

## Pharmacological interventions

Medications with a longer history that have disease-modifying potential – that they can retard or prevent the rate of radiographic damage to joints – include glucocorticoids as well as conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), the most commonly prescribed being methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Unlike csDMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) improve certain features of inflammation, particularly symptoms of stiffness and pain, but have no capability to modify the rate of structural damage to joints in human disease.

The last few decades have witnessed unprecedented advances in our understanding of the pathophysiology of RA and this has been translated into a broad range of efficacious, so-called 'targeted', therapies directed against relevant cells and molecules contributing to disease expression. These include parenterally administered biologic disease modifying anti-rheumatic drugs (bDMARDs) and orally available targeted synthetic disease modifying anti-rheumatic drugs (tsDMARDs).

There are four different classes of currently approved bDMARDs comprising tumour necrosis factor (TNF) inhibitors, antibodies directed against interleukin 6 receptor (IL6R), antibodies directed against the CD20 antigen expressed on a B cell subset and an inhibitor of the CD28-CD80/86 co-stimulatory signal necessary for T cell activation.[6]

## bDMARDs

The first generation of bDMARDs, referred to as bio-originators, were approved with finite patent life. Following patent expiry of the earliest bio-originator bDMARDs, biosimilars have emerged. A biosimilar is a biologic medicinal product that is highly similar to an already authorised original biologic (reference medicinal product or bio-originator) in terms of quality, safety and efficacy, based on a comprehensive comparability exercise. Following their introduction to the clinic, high procurement costs of bio-originator bDMARDs have presented a challenge to access in many health care economies. In the case of the anti-TNF bDMARD class, bio-originators included three monoclonal antibodies (infliximab, adalimumab and golimumab), a TNF receptor fusion protein (etanercept) and a pegylated antibody-binding fragment →

(certolizumab). There are now several biosimilars of infliximab, etanercept and adalimumab which are introducing cost-competition and facilitating wider access to the anti-TNF bDMARD class. Similarly, in the case of rituximab, an anti-CD20, there are now several approved biosimilars. As of the time of writing, there are two bio-originator anti-IL6R monoclonal antibodies (mAbs), tocilizumab and sarilumab (biosimilar anti-IL6R mAbs are in development), and one bio-originator directed against CD80 and 86, abatacept, a fusion protein composed of the Fc region of the human IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).

### tsDMARDs

In contrast to bDMARDs, which are large molecular weight proteins that must be injected and are incapable of penetrating the lipid bilayer of cell membranes, tsDMARDs are low molecular weight, orally available, 'small-molecules'. The only tsDMARDs currently available for the treatment of RA are inhibitors of Janus kinase (JAK) enzymes, a family of four intracellular tyrosine kinases that function in the cytoplasmic intracellular signalling cascade of the Type I/II family of cytokines and for certain growth factors after engagement with their receptors. JAK inhibitors are multi-cytokine inhibitors that can cross the cell membrane to block activity of one or more cytoplasmic JAKs. There are currently four JAK inhibitors approved in Europe for treatment of active RA.[7] Tofacitinib selectively inhibits JAK1 and JAK3 and was the first JAK inhibitor to be approved, initially with twice daily dosing. A modified release formulation for once daily use has since been developed. Baricitinib selectively inhibits JAK1 and JAK2 and is dosed once daily. Filgotinib is a once-daily preferential JAK1 inhibitor and upadacitinib is also a once daily dose with selectivity for JAK1. All four drugs have undergone extensive clinical trials and demonstrated rapid improvements in symptoms and signs when used in combination with concomitant methotrexate, other csDMARDs, or as monotherapy. All four agents inhibit structural damage progression and when used in combination with concomitant methotrexate, they demonstrate at least comparable efficacy to that of biologic anti-TNF used in combination with concomitant methotrexate.[8–11]

## Pharmacological management and standard of care treatment recommendations

### csDMARD treatment initiation

The European Alliance of Associations for Rheumatology (EULAR) recommends early initiation of treatment with csDMARDs on presentation with RA, which should most commonly be with methotrexate unless there are contraindications.[12] Based on its efficacy, safety, large dose-titratable range, options for either an oral or parenteral route of administration, and cost-effectiveness, methotrexate (MTX) holds a unique place in the management of RA.[13] MTX monotherapy is recommended as an initial pharmacological strategy, but many patients do not achieve and sustain treatment targets with MTX alone. Folic acid supplementation is recommended for all patients treated with methotrexate as it improves tolerability and reduces the potential for haematological and hepatic toxicity.[13] Short-term use of bridging glucocorticoid should be considered when initiating or changing csDMARDs with a variety of dose regimens and routes of administration to choose from. However, glucocorticoids should be tapered and then discontinued as rapidly as clinically feasible to avoid any of the many undesirable adverse effects associated with long term use.[12] MTX can also be used as an 'anchor drug' in combination with other csDMARDs, any bDMARD, or any tsDMARD.

### Initiation of first-line targeted therapy

If the treatment target is not achieved with the primary csDMARD treatment after three to six months, or if poor prognostic factors are present (such as high disease activity, rheumatoid factor positivity, presence of ACPA, or erosions), or the patient has already failed to respond adequately to a combination of two or more csDMARDs, a bDMARD or tsDMARD should be considered. If the treatment target is subsequently achieved, without unacceptable adverse events, then this will establish an appropriate regime for the individual. In the case of those who achieve and sustain a treatment target, particularly one of remission, consideration may be given to tapering any background csDMARD or even to tapering the targeted therapy.[12]

The choice of initial targeted therapy will depend on several factors, including the patient's preference for route of administration and dosing frequency, the patient's age, whether the targeted therapy will be used in combination with MTX (or other csDMARD) or as a monotherapy, and considerations of benefit versus potential risk. EULAR recommendations for RA management following inadequate response to optimised therapy with csDMARDs in patients with poor prognosis give equal status to bDMARDs and tsDMARDs with the caveat that JAK inhibitors should only be initiated after a careful assessment of potential risks in the context of the individual medical history.[12] Historically, as the first class of biologics to have reached the clinic, anti-TNFs have accounted for the majority of first-line targeted therapies for RA treatment, and this may have increased further due to their increased cost-effectiveness following the introduction of biosimilars.[14,15]

Biologic therapy would usually be added to background methotrexate (or other csDMARD) in the first instance. However, more than a third of patients experience tolerability problems on methotrexate, particularly when it is orally administered. Consequently, about a third of patients in clinical practice receiving treatment with a bDMARD eventually take it as monotherapy.[16] All bDMARDs demonstrate better efficacy when combined with concomitant methotrexate as compared with use as monotherapy. This may be due to complementary mechanisms of action, pharmacokinetic interactions, and reduction in immunogenicity of the administered bDMARD. Therefore, if a patient is intolerant of high dose methotrexate, rather than substituting a bDMARD, it is worth considering reducing the methotrexate dose to a tolerated level and adding a bDMARD. In clinical studies of methotrexate used in combination with the anti-TNF agent adalimumab, oral methotrexate at 10mg weekly was reported to give similar clinical outcomes and bDMARD pharmacokinetic profiles as 20mg weekly.[17]

In general, based on indirect comparisons, approved bDMARDs have similar efficacy when used in combination with methotrexate.[18] In a direct comparison, the efficacy of abatacept and adalimumab were compared in methotrexate-inadequate responders and bDMARD-naïve patients who continued background MTX.[19] The efficacy and kinetics of response of both bDMARDs, despite the different mechanisms of action, was remarkably similar. At present there is a paucity of data supporting evidence-based prioritisation of currently available bDMARDs of different mechanisms of action when used in combination with concomitant MTX. This situation highlights the need for a research agenda for identification of

treatment stratifiers that enrich for the most favourable benefit:risk profiles and provide the most cost-effective care. In the case of patients for whom a monotherapy bDMARD choice is preferable over combination therapy, in head-to-head studies, inhibition of IL6R gives rise to superior efficacy outcomes than TNF blockade.[20,21] In circumstances in which monotherapy is preferred, the EULAR recommendations prioritise use of either bDMARDs targeting IL6R or oral JAK inhibitors, having taken a careful risk assessment into account, over TNF inhibition[12].

Many patients, and particularly those with a short disease duration, rank oral administration as their preferred mode of treatment.[22] At present, JAK inhibitors represent the only class of orally available, small molecule targeted therapies. All approved JAK inhibitors offer rapid and significant improvements in efficacy measures, including patient reported outcomes, with particularly striking improvements in pain.[8–11] JAK inhibitors have recently been in the spotlight due to a possible class effect associated with certain adverse events, such as major adverse cardiac events (MACE), venous thrombotic events (VTE), and malignancy. However, lack of controlled comparative data has led to clinical difficulty in making relative benefit-risk assessments among alternative treatment options with different mechanisms of action.
A randomised study of patients with RA aged 50 years or older enriched for cardiovascular risk factors, ORAL Surveillance, reported a small increased risk of MACE and malignancy, which did not meet non-inferiority criteria, as well as higher incidences of serious infection, VTE, and all-cause mortality in patients being treated with tofacitinib compared with TNFi-treated patients.[23] It is not yet known whether these relative risk differences between a JAK inhibitor and biologic anti-TNF represent a class effect. In a post hoc analysis of ORAL Surveillance, high risk of these adverse events was confined to patients defined by distinct risk factors age ≥65 years or smoking.[24] The EULAR recommendations for management of RA propose that such risk factors, including a history of atherosclerotic cardiovascular disease, are taken into account before considering the use of any JAK inhibitor.[12] Of course, the likelihood of benefit and chance of risk, based on the unique clinical picture of any individual with RA, needs to be taken into account in the choice of any drug.

**Second line targeted therapy**

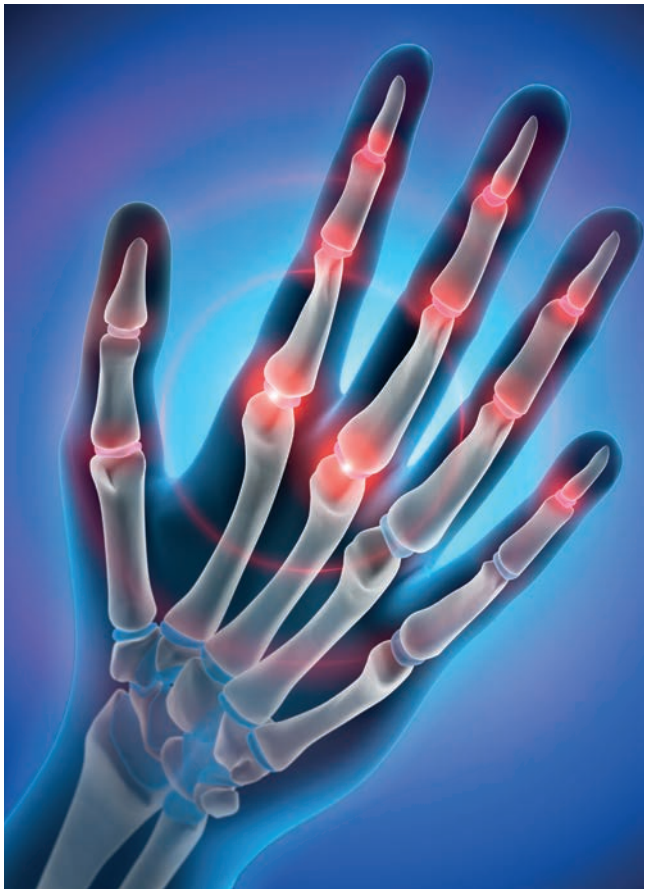
Although anti-TNFs are established as a favoured first-line biological therapy for RA with over two decades of accumulated clinical experience and well known efficacy/safety profiles along with additional benefits on various comorbidities, up to 40% of patients may respond inadequately to an initial anti-TNF treatment because of primary non-response, loss of response, or intolerance.[25] Following inadequate response to anti-TNF treatment, clinicians can consider switching to an alternative anti-TNF (cycling) or to another class of targeted drug with a different mechanism of action (switching). A proportion of patients failing to respond to a first anti-TNF will attain a response to a second agent, whether administered after a delay[26] or immediately as in the EXXELERATE trial which confirmed highly similar efficacy and safety on comparing two different anti-TNFs, certolizumab pegol and adalimumab, both administered with background MTX.[27]

As a general rule, the level of efficacy with any targeted therapy tends to be less when used after a first TNFi failure than when used as a first line bDMARD. As the number of approved and efficacious treatments with distinct mechanisms of action has expanded in recent years, contemporary practice favours switching to a non-TNF bDMARD or a tsDMARD if a second biologic TNF inhibitor fails.[12] In the absence of precision medicine biomarkers with the potential to reliably inform a treatment choice, it is important that rheumatologists practise 'personalised' medicine, taking into account relevant factors that may influence treatment →

choice.[28] These include the predominant symptomatology, any comorbidities the patient may have (or be at risk of developing), the level of disease activity and whether or not it is seropositive, lifestyle and preference for route of administration, as well as the age and sex of the patient. For example, there are special considerations for women of childbearing age who express a pregnancy wish. In every case, careful consideration must be given to the likelihood of benefit and that of risk, and its acceptability to the individual living with RA.

## Conclusion

Pharmacological management of RA aims to optimally suppress the inflammatory component of the disease with an ideal treatment target of remission. Early therapeutic intervention has unequivocal long-term benefits in prevention of disability and preservation of quality of life. But once RA becomes established, a target of low disease activity may be more realistic, and the physician and patient need to work together to determine what is safe and achievable for that individual with a view to minimise symptoms and signs, prevent progression of joint damage, preserve and improve function, while preventing and treating co-morbidity and reducing RA-associated mortality. As many patients will experience an inadequate response to a given treatment at some point during their disease, it is essential to adjust pharmacotherapy as required so that the best outcomes for the patient are achieved within the shortest possible timeframe. As a consequence of early intervention, the advent of highly efficacious targeted therapies and a treat-to-target approach to management, the outlook for people presenting with RA has improved dramatically over the last generation.

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# Impact of biosimilars on immune-mediated diseases

Development of biosimilars represents a key milestone in increasing the cost-effectiveness and accessibility of biological therapies; however, hesitancy in prescribing and/or switching patients to these drugs remains a barrier to realising their full potential

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Biosimilars are biologics that replicate reference medicines that have received regulatory approval and where the patent has expired.[1–3] The availability of biosimilars over recent years has reduced the economic burden of biological therapies and increased patient access to treatments.[1–3] Despite the advantages offered by biosimilars, there are barriers to uptake of these agents among healthcare professionals and patients.[2,4]

## Evolution in use of biologics

The introduction of biologic medicines in the 1980s revolutionised the treatment of many chronic and often disabling diseases, including autoimmune disorders such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease.[3,5,6] Biologics targeting anti-tumour necrosis factor (i.e., anti-TNF drugs) are among the most commonly used such therapies, and may be used to reduce inflammation and halt disease progression across a range of conditions in rheumatology (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile arthritis), gastroenterology (e.g., Crohn's disease, ulcerative colitis), and dermatology (e.g., psoriasis, hidradenitis suppurativa).[7] However, these agents impose a considerable financial burden on healthcare systems and are key drivers of direct healthcare costs,[8] with results of a systematic review showing that the introduction of biologics led to a 3–5-fold increase in direct costs of psoriasis and psoriatic arthritis in five European countries (Germany, Spain, France, Italy, and the UK).[9]

The relatively high costs of biologics can result in delayed treatment initiation and increased treatment burden.[6] Strict reimbursement criteria limit access in several countries, and, as a consequence, inequalities in access to treatment may be observed.[6,10]

The first biosimilar was approved in Europe in 2006, and over 80 biosimilars have subsequently received European marketing authorisation.[3,4,11] Biosimilars have contributed to reduced R&D costs compared with reference biologics, and can therefore make available more cost-effective treatment options. These therapies can potentially increase market competition, improve patient access, and support the sustainability of healthcare systems.[3,6,12,13] Indeed, published data for Europe show reductions in treatment price within established therapy areas with biosimilar competition.[12] For instance, infliximab and etanercept biosimilars were estimated to have saved rheumatology specialties in the National Health Service (NHS) in the United Kingdom approximately £39 million between March 2014 and February 2017.[14]

In addition to providing potential cost savings, biosimilars can increase the number of treatment options available to patients and clinicians.[15] There are also opportunities to develop innovative biosimilars that add value; for instance, providing more convenient (e.g., subcutaneous vs intravenous formulation) or longer-acting drug formulations.[2] Despite the accumulating clinical experience with biosimilars and the growing body of real-world evidence, barriers to the uptake of these agents remain.[2,16]

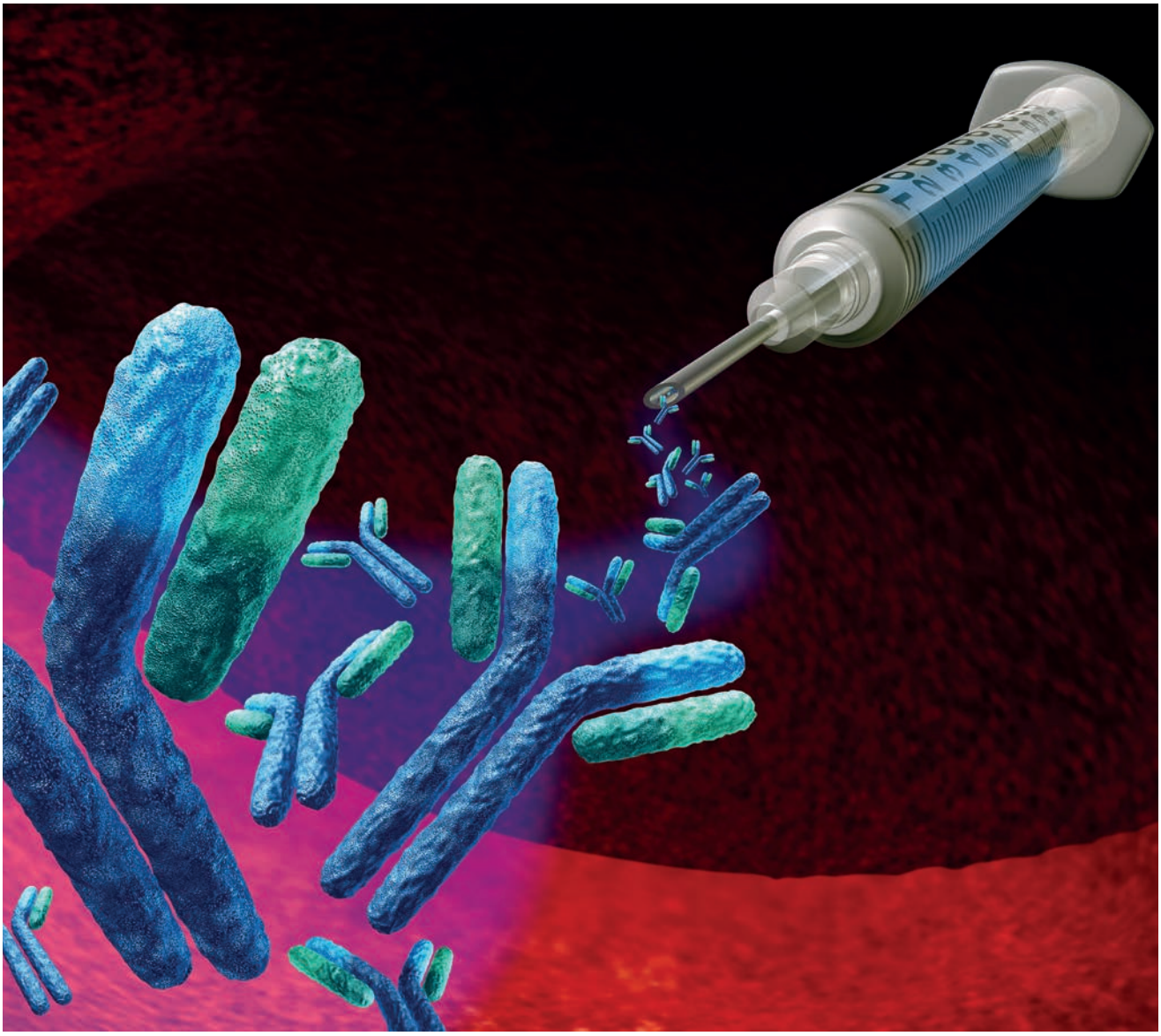
## Similarity between biosimilars and reference biologics

As biosimilars are produced by living cells (e.g., human, bacteria, or yeast), they are by virtue only highly similar to their original reference product, in contrast to generics which are chemically synthesised and identical to the original reference product.[1,3] The high levels of similarity of a biosimilar to its reference biologic relates to structure, biological activity, efficacy, safety and immunogenicity, and regulatory frameworks are in place to ensure that there are no clinically meaningful differences between biosimilars and reference products.[2,3] Biosimilars approved in Europe are interchangeable, which means there is potential to replace one drug with another that is considered to have the same clinical properties.[3,5]

## Access to biosimilars

In 2020, biosimilar medicines represented 9% of the total European biologics market in terms of treatment days; however, access varies between countries because of differences in national guidelines, funding, and care pathways.[7,17] For instance, within the anti-TNF market, there is considerable biosimilar competition, but market share analysis in 2017 showed infliximab biosimilars held 79% of the market share in the UK, compared with 33% and 40% in France and Spain, respectively.[12]

Decisions regarding switching biosimilars for reference biologics are regulated at a national level.[5] In Italy, Germany and the United Kingdom, responsibility for administering a reference biologic or its biosimilar is the responsibility of the prescribing physician; while in France, biosimilars may be used in patients who are naive to biologics, and in Denmark, national guidelines mandate a switch from reference anti-TNFs to biosimilars in patients with inflammatory rheumatic diseases.[5,17,18] Greater access to biosimilars may result in better patient outcomes, as earlier use of biologic therapies may be associated with clinical benefits and potentially reduced healthcare costs.[17] Consequently, there are national programmes to incentivise biosimilars prescribing, →



including the National Institute for Health and Care Excellence (NICE) recommending that British rheumatologists begin treatment using the least expensive option, and quota systems in Germany and Belgium requiring biosimilars prescriptions in up to 40% of patients.[11]

### Barriers to widespread adoption of biosimilars

#### Healthcare professionals

Physicians' concerns regarding switching include the potential for increased immunogenicity, for increased consultation time prior to switching, and the need to extrapolate efficacy and safety data to different indications.[13,16] Extrapolation refers to approval of a biosimilar for clinical indications of the reference biologic without the need to conduct clinical trials with the biosimilar in these other indications;[5] it represents a key part of minimising drug development and regulatory approval costs of biosimilars.[2] Results from a 2015 survey of European gastroenterologists support immunogenicity being a key concern (69% of respondents) and approximately half of respondents were in agreement with extrapolation across indications without direct clinical evidence.[16]

Despite concerns regarding immunogenicity, there are no known reports of an increase in immunogenicity in patients receiving a biosimilar developed to the standards of the FDA or the European Medicines Agency (EMA).[11] Furthermore, real-world evidence from DANBIO – the national registry in Denmark – found no obvious changes in healthcare utilisation and costs in patients who were switched from infliximab to biosimilar infliximab,[19] or from etanercept to biosimilar etanercept in routine care.[18] Published switching studies have reported consistent efficacy and safety when switching between reference biologics and biosimilars.[17] A systematic review evaluating the efficacy and safety of biosimilars of anti-TNF agents in patients with IBD reported that CT-P13 – the first anti-TNF monoclonal antibody to obtain approval in Europe – was non-inferior compared with its reference biologic, infliximab.[20] These data are also supported by real-world evidence from registries (e.g., DANBIO) and observational studies,[13] in addition to post-marketing studies, such as the NOR-SWITCH study.[21] This Phase IV study has demonstrated no difference in safety and efficacy through 78 weeks between patients who switched from infliximab to its biosimilar CT-P13 and patients receiving continuous CT-P13. The study shows that patients receiving infliximab can be safely switched to biosimilar therapy, while maintaining a prolonged response with minimal adverse effects. Notably, no

significant differences in immunogenicity were observed during the 78-week trial period.[21] Nonetheless, further studies will be required to add to the existing evidence base.[13,16]

### Patients' concerns

Switching to biosimilars may also represent a concern for patients, and has been associated with a possible nocebo effect, whereby negative effects with a medical treatment (e.g., loss of efficacy, adverse events) are induced by patients' expectations and are unrelated to the mechanism of action of the intervention.[13,15] This signifies an important clinical challenge that may reduce the acceptance of, and clinical benefits with, biosimilars, and may ultimately limit their incorporation into routine clinical practice.[13] This effect may also lead to increased discontinuation rates,[13] and some support for this was observed in real-world data from the DANBIO registry data, which showed slightly lower retention rates in patients with rheumatoid arthritis who were switched to biosimilar compared with a historical cohort of infliximab-treatment patients.[22]

Joint decision-making between physicians and patients is a key aspect initiating treatment with a biosimilar;[13] it is therefore important to manage patients' expectations to reduce the risk of nocebo effects.[15] 'Non-medical switching' also represents a concern for patients, and refers to a change in a patient's drug (e.g., switching from a reference biologic to its biosimilar) for cost-saving purposes as opposed to medical reasons.[5]

### Role of education in increasing access to biosimilars

While confidence in prescribing biosimilars has increased overall (e.g., in surveys of European gastroenterologists, 61.0% reported little/no confidence in biosimilar prescribing in 2013 compared with 19.5% in 2015),[16] there is an unmet need to address physician concerns about biosimilars.[5] Although physicians consider educational activities on biosimilars fundamental,[16] there are considerable gaps in patients' knowledge regarding biosimilars.[4,17] There is also a lack of consistent information on biosimilars between member European countries, and some member countries do not offer any information about biosimilar medicines.[4] To address this, educational materials on biosimilars are now available for healthcare professionals and patients in all 23 official European languages to support more consistent messages and education on biosimilars.[3]

Improving the understanding of biosimilars among healthcare professionals may also be beneficial by increasing trust and familiarity with biosimilars, increasing confidence in prescribing, maximising cost savings, and improving patient access.[2,17] With the increasing evidence base to support a role for biosimilars, evidence-based approaches may be used to help allay physicians' concerns about indication extrapolation and switching from reference products.[2]

Unmet needs in patient education may impact patients' willingness to receive biosimilars.[23] Patient-centred information on the quality, efficacy and safety of biosimilars compared with reference biologics (e.g., lay summaries) could be used to address patient concerns.[23,24] These materials could be developed by medical societies or government organisations, in collaboration with patient advocacy groups.[2,23]

### Conclusion

Development of biosimilars represents a key milestone in increasing the cost-effectiveness and accessibility of biological therapies.[1–3] However, hesitancy in prescribing and/or switching patients to biosimilars remains a barrier to realising the full potential of these agents.[4,13,16]

To increase the acceptance of biosimilars and to accelerate their integration into clinical practice, a greater focus on education for both patients and prescribers is required. Patient- and prescriber-directed education will boost confidence in prescribing and uptake, and facilitates effective communication about the role of biosimilars in optimising patient care.[2,16] More widespread acceptance of anti-TNF biosimilars across healthcare systems through their impact on healthcare sustainability and cost benefits, and timely approvals, will enable more equitable treatment access and help optimise chronic immune-mediated disease management.[6]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# Impact of pharmacist care and interventions in patient management and education

The effective management of immune-mediated inflammatory disorders (IMIDs) requires multidisciplinary care involving physicians, nurses, pharmacists and others. This article focuses on the role and impact of pharmacist care in patients with IMIDs

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Immune-mediated inflammatory disorders (IMIDs) such as inflammatory arthritis, psoriasis and inflammatory bowel disease (IBD) significantly affect patients' quality of life and place a considerable burden on healthcare systems worldwide. IMIDs are complex and can be difficult to manage. Patients' disease knowledge is critical in the effective management of IMIDs as it allows them to be active participants in their care, make informed decisions, and adhere to their treatment regimens. Patient education is a crucial component of pharmacist care for patients with IMIDs. Pharmacists can provide patients with a better understanding of their condition, the treatment options, potential side effects and self-management strategies. This can help patients make informed decisions about their care and improve their ability to self-manage their condition.

A systematic review and meta-analysis showed that pharmacist-led educational interventions improved medication adherence and clinical outcomes for patients with rheumatoid arthritis,[1] with similar results seen in patients with IBD.[2] These interventions have been demonstrated to improve patients' understanding of their condition, their medication, potential side-effects and the importance of adhering to the treatment plan.[3,4]

### Medication adherence and management of side effects

Non-adherence to prescribed medicines is a significant challenge in the treatment of most conditions and can lead to suboptimal clinical outcomes, increased healthcare costs, and reduced quality of life for the patient. Pharmacists can help improve medication adherence by educating patients about the importance of taking their medications as prescribed, providing information about potential side effects, and offering strategies to overcome barriers to adherence. Pharmacist-led interventions such as medication reviews and counselling sessions are an effective intervention to improve adherence among patients with rheumatoid arthritis,[5] and pharmacist-led medication therapy management (MTM) services improved adherence in patients with Crohn's disease.[6] The medicines used to treat IMIDs can have significant side effects, including gastrointestinal problems and immunosuppression leading to an increased risk of infections. Pharmacists can play a critical role in managing these side affects and providing appropriate support to patients. They can offer advice and education on the use of non-pharmacological therapies such as diet and exercise and can also advise patients on the use of other medications to relieve side-effects and alleviate symptoms such as pain. They can also work closely with other members of the clinical team to make appropriate adjustments to medication regimes to minimise side effects, avoid drug interactions and consider patient factors such as frailty and renal impairment.

### Optimising treatment outcomes and quality of care

A number of studies have demonstrated that improving adherence to medication through pharmacist interventions also improves treatment outcomes.[1,2] However, pharmacist interventions can also improve the quality of care that patients with IMIDs receive. Pharmacists are well-placed to undertake comprehensive reviews of patients' medication, including prescription and non-prescription medicines and supplements. These reviews can identify potential drug interactions, duplicate therapy, and medication-related problems such as declining renal function. Improved quality of care can be difficult to manage; Alrashed et al surveyed patients and physicians at an IBD clinic which had implemented pharmacist-led clinics to improve quality of care, and found that both groups were satisfied or highly satisfied with the input of pharmacists into patient care.[7] Furthermore, Sahni et al reported how the establishment of a pharmacist-led biologic clinic in rheumatology improved the quality of care by reducing the delay in starting patients on biologic therapies.[8]

### Health-related quality of life, patient rehabilitation and satisfaction

A growing body of evidence suggests that pharmacist interventions can positively impact health-related quality of life (HrQoL), rehabilitation and satisfaction. Although there is limited evidence relating this to the IMIDs, previous studies in hypertension[9] and diabetes[10] have been shown to improve HrQoL by reducing pain, fatigue, and other symptoms that can also occur in IMIDs. This may also contribute to greater involvement in rehabilitation as patients will be more able to participate in physical therapy other activities that promote functional recovery.[11]

Pharmacist interventions can enhance patient satisfaction by providing personalised care and support,[12] with patients who receive pharmacist-led education reporting greater satisfaction with their healthcare experience.[13]

### Economic benefits

Pharmacist-led care has been demonstrated to improve disease control and reduce disease activity in patients with a range of IMIDs.[14,15] It has been estimated that pharmacist-led medication management in patients with rheumatoid arthritis leads to

significant cost-savings and improved outcomes, with a return-on-investment of $7.90 for every $1 spent.[16] Pharmacist care can also reduce the frequency of hospitalisations and emergency department visits related to IMIDs.[4] Improving disease control (for example, through improved adherence) can also result in decreased work absenteeism and increased productivity in patients with IMIDs, further contributing to the economic benefits.[17]

### Importance of the pharmacist in the multi-disciplinary team

As discussed above, pharmacists can play a key role in improving the care of patients with IMIDs by counselling and advising patients on their condition, medication, and treatment plans. They also undertake medication management functions by reviewing treatment and identifying problems including side-effects, drug interactions, and the need for dose adjustments to reflect changes in the patient's condition. The unique expertise and accessibility of pharmacists make the invaluable members of the multi-disciplinary team. They collaborate with physicians and other healthcare professionals to develop and implement individualised treatment plans for patients with IMIDs. Pharmacists can also contribute to the development of clinical guidelines, protocols, and pathways, ensuring that the care provided to patients is based on the best-available evidence.[18]

### Future developments

Biosimilars are biological medicines that are highly similar to, and have no clinically meaningful differences from, an existing approved reference product. The European Medicines Agency issued a statement in April 2023, and now consider biosimilars to be interchangeable with each other and the reference product.[19] Biosimilars provide a cost-effective alternative to some of the more expensive biologic therapies for the treatment of IMIDs, and this has already resulted in increased access to some biologics for patients – for example, patients with rheumatoid arthritis in the UK previously only had access to biologics if they had highly-active disease (defined as a DAS-28 of > 5.1) and had failed two or more conventional medications.[20] The availability of biosimilars changes the cost:benefit ratio and biologics are now available in the UK to patients with moderate disease activity (DAS-28) provided they have failed to respond to two or more conventional medications.

Pharmacogenetics and -genomics consider the influence of genetic variations on the response to medicines. Understanding the relationship between an individual's genome and their response to medicines has the potential to revolutionise the treatment of IMIDs, allowing for personalised therapy. Pharmacists are likely to be at the forefront of incorporating genetic information into clinical practice, which should guide the selection of medicines for optimal efficacy and safety.[21]

Therapeutic drug monitoring (TDM) involves the measurement of drug concentrations in the blood to optimise dosing and improve treatment outcomes. There can be significant inter-patient variability in the response to, and pharmacokinetics of, biologics; TDM can help pharmacists to identify the most effective dosages for individual patients or guide the decision to switch to an alternative medicine.[22]

### Conclusion

Pharmacists play a crucial role in the management of IMIDs, and their involvement can lead to improved adherence to medication, treatment outcomes and quality of care. There is the potential for pharmacists to be involved at all stages of the care pathway, from educating and counselling patients when they are newly-diagnosed and starting or switching treatment, through to monitoring for side effects or drug interactions, and adjusting medication regimens as the need arises. The involvement of pharmacists can also improve patient satisfaction and bring economic benefits through reducing admissions and other demands on the health service and contribute to patients being able to remain in work and economically active.


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