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Emerging treatment options for extraintestinal manifestations in IBD

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Abstract

Extraintestinal manifestations (EIMs) are frequently observed in IBDs and contribute considerably to morbidity and mortality. They have long been considered a difficult to treat entity due to limited therapy options, but the increasing use of anti-tumour necrosis factors has dramatically changed the therapeutic approach to EIM in recent years. Newly emerging therapies such as JAK inhibitors and anti-interleukin 12/23 will further shape the available armamentarium. Clinicians dealing with EIMs in everyday IBD practice may be puzzled by the numerous available biological agents and small molecules, their efficacy for EIMs and their potential off-label indications. Current guidelines on EIMs in IBD do not include treatment algorithms to help practitioners in the treatment decision-making process. Herein, we summarise knowledge on emerging biological treatment options and small molecules for EIMs, highlight current research gaps, provide

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therapeutic algorithms for EIM management and shed light on future strategies in the context of IBD-related EIMs.

INTRODUCTION

Extraintestinal manifestations (EIMs) are frequently observed in IBDs. Their reported prevalence ranges from 6% to 47% depending on the studied population and the definition of EIM.[1–7] Involvement of the following four organs are mostly considered as classical EIMs: joints (axial spondyloarthropathy, peripheral arthritis); skin (erythema nodosum (EN), pyoderma gangrenosum (PG), Sweet's syndrome, oral aphthous ulcers); liver and biliary tract (primary sclerosing cholangitis (PSC)); and eyes (uveitis, episcleritis).[8 9] In contrast, immune-mediated inflammatory diseases (IMIDs) such as psoriasis or rheumatoid arthritis are associated with IBD, but typically are not considered an EIM.[10] The frequency of EIM increases with longer disease duration, and the presence of one EIM predisposes for the development of further EIMs.[7] Some EIMs are associated with intestinal disease activity (such as pauciarticular peripheral arthritis, EN, Sweet's syndrome, oral ulcers and episcleritis), while others do not parallel intestinal IBD activity.[9] The latter group includes axial spondyolarthropathy and polyarticular peripheral arthritis of the small joints. The remaining EIMs may or may not parallel IBD activity, such as seen for PG, uveitis and PSC.[9]

EIMs should be treated since they considerably affect morbidity and mortality of patients with IBD.[11 12] In addition, EIMs are associated with higher disease activity, increased risk of surgery and increased need for treatment escalation.[13 14] Before the implementation of biologics, treatment options had been quite limited. The increasing use of anti-tumour necrosis factor (anti-TNF) and newly available biologics, small molecules have dramatically changed the therapeutic approach in EIM management. These drugs have been approved for various indications beyond IBD such as for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis or uveitis. Nevertheless, data on their emerging use as EIM treatment are still sparse. Analysing EIM treatment in a prospective manner is difficult, since only few patients present with EIMs at study enrolment.[8] To some degree, findings from IMIDs treated with biologics and small molecules—particularly randomised controlled trials in rheumatology and dermatology—might be extrapolated.

This review summarises knowledge on emerging biological treatment options and small molecules for EIM (table 1, figure 1), highlight current research gaps, provide therapeutic algorithms for EIM management and shed light on future strategies in the context of IBD-related EIMs.

ANTI-TNF

TNF-dependent mechanisms in EIM pathophysiology are the rationale for the use of anti-TNF therapeutic approaches. Clinical data suggest good response rates for cutaneous manifestations, arthritis and ocular EIM with several interventional and non-interventional studies available.[15–17] Although no head-to-head comparisons have been performed, retrospective analyses suggest similar efficacy of anti-TNF agents.[16] Slight, but non-

significant differences appear to be attributed to the fact that adalimumab and certolizumab pegol are more often second-line and third-line treatments compared with infliximab.

Infliximab

So far, the only randomised placebo controlled trial in EIM has been conducted with infliximab (5 mg/kg), where 30 patients with PG (19 patients with IBD) were treated for 2 weeks.[18] Clinical improvement was achieved in 46% versus 6%. In addition, several open-label studies have been published using infliximab (5 mg/kg) in EIMs with clinical remission rates of 33%–46% (arthritis, inflammatory arthralgia), 21%–25% (PG), 100% (uveitis, cutaneous manifestations), and improvement rates of 60%–80% (arthritis, inflammatory arthralgia), 63.6% (inflammatory back pain) and 69%–100% (PG).[18–21] Generini *et al* further showed decreasing prevalence rates of arthritis after 6 months of infliximab treatment (from 58% down to 12.5%).[22] Several retrospective studies (sample size 13–54 patients) are consistent with these data with improvement rates of 70%–100% for cutaneous and joint manifestations and remission rates of 25%–38% (cutaneous/joint manifestations) and 92%–100% (PG).[23–25] A comprehensive analysis of infliximab-treated EIMs (musculoskeletal, ocular and cutaneous manifestations) in 189 patients enrolled in the Swiss IBD cohort study revealed clinical improvement rates of 74%.[16]

Adalimumab

Adalimumab (induction dose 160/80 mg, then 40 mg every 2 weeks) has been prospectively studied in the context of EIMs and demonstrated decreasing frequencies of arthritis (from 8.7% to 2.1%), sacroileitis (from 3.6% to 1.9%) and EN (from 2.4% to 0.4%) after a 20-week treatment.[26] Six-month treatment resulted in improvement/remission rates of 61% (arthritis, n=7) and 100% (ankylosing spondylitis, n=1; uveitis, n=1; and PG, n=2).[27] PG remission rates were 100% in the retrospective study conducted by Argüelles-Arias *et al* (n=7).[24] The Swiss group revealed overall response rates of 70% for adalimumab-treated EIMs in 67 patients.[16]

Other anti-TNFs

The only study looking at IBD-related EIMs treated with certolizumab pegol was an analysis of the Swiss IBD cohort, where response rates were reported as 56%.[16] The pegylated anti-TNF agent has been approved for other IMIDs such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis suggesting efficacy in IBD-associated musculoskeletal manifestations. Reported improvement rates from phase III trials were 57.3%–60.8% (vs placebo 8.7%–13.6%) for rheumatoid arthritis at week 24,[28 29] 51.9%–58.0% (vs placebo 24.3%) for psoriatic arthritis at week 12[30] and 57.7%–63.6% (vs placebo 38.3%) for ankylosing spondylitis at week 12.[31] A post hoc analysis of the RAPID-axSpA trial revealed significantly lower rates of uveitis flares with certolizumab pegol compared with placebo (3.0 vs 10.3 per 100 patient-years).[32] In addition, uveitis was successfully treated in five of seven patients with previous failure to another anti-TNF agent.[33]

While no data are available for golimumab's efficacy in EIM management, data from trials with patients suffering from other IMIDs may be extrapolated. In phase III trials, the following response rates have been described: 71.1% for ankylosing spondylitis at week 16

(vs placebo 40%)[34]; 51.0% for psoriatic arthritis at week 14 (vs placebo 9.0%)[35]; 61.6% for methotrexate (MTX)-naive rheumatoid arthritis after week 14 (vs 49.4% for MTX alone)[36] and 55.1%–74.7% for MTX-experienced rheumatoid arthritis (vs 27.3%–33.1% for MTX alone).[37 38] Golimumab treatment has been recently shown to significantly reduce the occurrence rate of acute uveitis in patients with ankylosing spondylitis (from 11.1 to 2.2/100 patient-years).[39] More lately, there has been a case report demonstrating resolution of pyostomatitis vegetans in a patient with UC who under treatment with golimumab.[40]

Taken together, anti-TNFs are an efficacious treatment option for IBD-related EIMs. While anti-TNF agents are probably equally effective, best evidence is available for infliximab (online supplementary table).

ANTI-INTEGRINS

Anti-integrins block the interaction between ligands on lymphocytes and their corresponding receptors expressed on endothelial cells. Thereby, they interfere with leucocyte adhesion and migration, ultimately inhibiting T-lymphocyte trafficking to the site of inflammation. Two agents have been approved for the treatment of IBD: natalizumab and vedolizumab.

Vedolizumab

The gut selective mechanism of the integrin α4β7 antibody vedolizumab should restrict its activity to the gut, since the adhesion molecule ucosal addressin cell adhesion molecule 1 (MAdCAM1), which acts as the counterpart of α4β7, is exclusively expressed in the GI tract. A recent analysis of cutaneous EIMs did not reveal overexpression of MAdCAM1 in skin biopsies from patient with EN and PG.[41] Nonetheless, vedolizumab treatment has been associated with successful resolution or at least improvement of EIMs, such as arthritis/arthralgia and EN in a recent prospective study.[42] Two hundred and ninety-four vedolizumab-treated patients were followed through week 54; 49 of those patients had at least one EIM at baseline. Clinical remission rates were 44.7% for arthritis/inflammatory arthralgia (n=47) and 75% for cutaneous manifestations (n=4). These findings were partially replicated in a recent post hoc analysis of the vedolizumab trials in IBD[43]: vedolizumab-treated patients with Crohn's disease (CD) were less likely to show new or worsening arthritis/arthralgia compared with placebo (HR=0.63). There are two possible explanations for these results: (1) vedolizumab has beneficial effects through a better control of intestinal disease therefore affecting EIMs that parallel intestinal disease activity. This is underscored by the fact that complete remission of musculoskeletal EIMs was associated with clinical remission of IBD in both studies[42 43] and (2) the positive effect of vedolizumab on disease activity of EIM could occur, if lymphocytes require the α4β7–MAdCAM1 interaction to gain access to the gut where they are activated, followed by non-α4β7-dependent entry to extraintestinal sites. However, the post hoc analysis of the GEMINI trials did not reveal a positive effect of vedolizumab in UC and sustained resolution rates between for arthritis/arthralgia were not significantly different from placebo (GEMINI trial III 22% vs 16%).[43] Moreover, a recent meta-analysis based on three interventional studies, five non-interventional studies and three case series concluded that as of yet there is no strong evidence for the efficacy of vedolizumab in the treatment of pre-existing EIMs.[44] Lately, an

ECCO CONFER series showed no response of PG, but partial response of EN.[45] However, the latter is based on four patients only and should therefore be interpreted cautiously. Taken together, vedolizumab should be used for the treatment of intestinal disease activity and not for EIM. However, it might be considered for EIMs (such as peripheral arthritis) if they clearly parallel intestinal disease and if intestinal inflammation is indeed present.

Natalizumab

Natalizumab has been studied for the treatment of multiple sclerosis and CD. Although approved for CD management, it has rarely been used in clinical practice given the potentially fatal side effects of progressive multifocal leucoencephalopathy.[46] Neither prospective nor retrospective studies have been conducted in IBD-associated EIMs. A study evaluating natalizumab for the treatment of rheumatoid arthritis failed to show efficacy and was terminated early (ClinicalTrials.gov NCT00083759). With regards to the potential of fatal side effects related to reactivation of the JC polyomavirus, natalizumab cannot be recommended in the setting of EIM.

Based on the available studies, anti-integrins are a possible treatment modality for IBD-related EIMs that parallel intestinal disease activity (online supplementary table). Natalizumab should not be used due to potentially deleterious side effects.

JANUS KINASE (JAK) INHIBITORS

JAK inhibitors are emerging oral agents for the treatment of IBD, rheumatological and dermatological disorders. Tofacitinib has been recently approved for UC in the USA and in Europe. Results from trials in rheumatoid arthritis and psoriasis are encouraging for its use in EIM management. Still, it should be kept in mind that positive results in the treatment of other IMIDs cannot be applied one to one to EIM management. Upregulation of STAT3 in EN and PG sheds light on the possible involvement of the JAK-STAT pathway in cutaneous EIMs and makes a response to JAK inhibitors reasonable to predict.[41]

Tofacitinib

Tofacitinib is approved for the treatment of UC, rheumatoid arthritis and psoriatic arthritis. Reported improvement rates from phase III trials for rheumatoid arthritis are 42%–71% after 3 to 6 months (placebo rate 24%–31%).[47–51] For psoriatic arthritis they are 47%–61% after 3 months (placebo rate 24%–33%).[52 53] For psoriasis they are 40%–64% after 12 to 16 weeks (placebo rates 6%–11%).[54 55] For ankylosing spondylitis, a phase II trial showed promising results with 12-week improvement rates of 52%–81% (placebo rate 41%).[56] A post hoc analysis of data from the OCTAVE Induction 1 and 2 and OCTAVE Sustain was recently published in abstract form suggesting some improvement of IBD-related peripheral arthritis by week 52, but low patient numbers did not permit any clear conclusions regarding the effect of tofacitinib on EIM symptoms (online supplementary table).[57] Nevertheless, upregulation of the JAK-STAT pathway has been demonstrated in cutaneous manifestations. Immunohistochemical analyses of skin biopsies from patients with PG and EN revealed overexpression similar to what was seen in intestinal samples from patients with IBD.[41] Indeed, upregulation of JAK-STAT was significantly higher in PG, EN compared with

psoriasis. The use of tofacitinib in PG has further been supported by a case report and by a case series involving three patients.[58 59] Very recently, tofacitinib has been successfully used to treat refractory uveitis and scleritis in two patients.[60]

Filgotinib

Filgotinib is a selective JAK-1 inhibitor currently under investigation for CD, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Phase II trials in rheumatic diseases revealed promising results with improvement rates of 64%–79% for rheumatoid arthritis (at week 12, vs placebo rate of 29% and 44%), 80% for psoriatic arthritis (at week 16, vs placebo rate of 33%) and 76% for ankylosing spondylitis (at week 12, vs placebo rate of 40%).[61–64]

Despite the lack of direct evidence for the efficacy of tofacitinib in treatment of IBD-related EIMs, positive trials in rheumatology and dermatology make tofacitinib an appealing treatment modality for cutaneous and musculoskeletal EIMs. However, efficacy in the treatment of IMIDs such as rheumatoid arthritis does not necessarily imply guaranteed efficacy in the treatment of EIM (such as peripheral arthritis). In addition, its use is restricted to patients with UC, as it has not been shown to be efficacious in CD treatment.[65]

ANTI-INTERLEUKIN 12/23 (IL-12/23)

The anti-p40 (IL-12/23) antibody ustekinumab is approved for the treatment of CD, UC, psoriasis and psoriatic arthritis. Few case series and case reports revealed improvement of IBD-associated arthritis and cutaneous manifestations (online supplementary table). Still, there are no prospective studies published regarding the efficacy of ustekinumab in the treatment of IBD-associated EIMs.[45 66–69] Phase III trials demonstrated improvement rates of psoriatic arthritis at week 24 of 42.4%–49.5% (compared with a placebo rate of 20.2%–22.8%).[70–72] Despite some initially promising results in the treatment of ankylosing spondylitis with improvement rates after 24 week of 65%, the phase III programme was early terminated due to the lack of efficacy.[73 74] Lately, ustekinumab has been successfully used in a patient with uveitis.[75]

Based on the available data (although not studied in true EIMs), ustekinumab appears to be a valuable option for musculoskeletal EIMs (peripheral arthritis) and might be considered for cutaneous and ocular manifestations in case other therapies fail. Given early termination of the phase III programme for ankylosing spondylitis, its use in this setting cannot be strongly supported.

OTHER ANTI-INTERLEUKINS

Further interleukins such as IL-17 or IL-6 have been successfully targeted in rheumatological and dermatological inflammatory disorders suggesting efficacy in EIM management also. The anti-IL-17 antibody secukinumab is approved for the treatment of psoriasis and psoriatic arthritis. Whether it has beneficial effects on joint and skin manifestations in IBD remains unknown. However—despite the pathogenic role of Th17 cells in the development of colitis—trials with anti-IL-17 have failed in IBD, reporting

an even higher adverse rate than placebo.[76] Moreover, in contrast to its efficacy in other inflammatory disorders, anti-IL-17 can even exacerbate IBD activity,[77] which highlights a distinct involvement of the IL-17 pathway in these entities. The anti-IL-6 antibody tocilizumab is indicated in the treatment of rheumatoid arthritis. Anti-IL-6 antibodies might also be effective in IBD.[78] Tocilizumab's main limitation is the increased risk of intestinal perforation in patients with IBD.[78]

Given better options with a more favourable safety profile, off-label use of secukinumab and tocilizumab to treat EIMs in patients with IBD cannot be recommended.

TREATMENT ALGORITHM

In 2016, the first ECCO consensus guideline on EIMs was published with a detailed description of each EIM and discussion of possible treatment options.[79] Except for axial spondyloarthropathy, these guidelines lack clear recommendations regarding a treatment algorithm and when, how to use biological and small-molecule therapies. A thorough meta-analysis of the efficacy of anti-TNFs for treatment of EIMs had not been available at that time.[15] Data on vedolizumab and JAK-inhibitors have emerged only very recently. Other societies such as the American Gastroenterology Association, American College of Gastroenterology, World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology do not have specific guidelines or recommendations for EIM management.

Treatment algorithms for musculoskeletal, cutaneous and ocular EIM

As a general principle, underlying intestinal disease activity should always be treated first, particularly for EIMs that clearly parallel IBD activity, such as pauciarticular arthritis or EN. Mild musculoskeletal disease can be treated using non-steroidal anti-inflammatory drugs (NSAIDs), but caution should be applied given their potential to worsen intestinal disease activity.[80 81] Selective COX-2 inhibitors are an alternative since they have not been shown to exacerbate IBD.[82 83] However, clinicians should keep their cardiovascular side effects in mind. Anti-TNFs should be initiated for refractory cases and/or intolerance to NSAIDs. Given the lack of clinical data on tofacitinib and ustekinumab in the treatment of IBD-associated EIMs, these drugs should preferably be used when initiated for underlying intestinal inflammation or in case of anti-TNF failure. For cutaneous manifestations, topical steroids might be sufficient. In case of severe disease, particularly PG, early use of anti-TNF should be considered regardless of intestinal disease activity. Best evidence is available for infliximab, but other anti-TNF agents are probably equally effective. Given the upregulation of the JAK-STAT pathway in both EN and PG, JAK inhibitors might be considered in the context of active intestinal inflammation, contraindications for anti-TNF and/or loss of response to anti-TNF. However, they represent an option in patients with UC only given their lack of efficacy in CD. Uveitis should always be seen as an ophthalmological emergency. Treatment should therefore be guided by an experienced ophthalmologist. Although uveitis may parallel intestinal disease activity, treatment of intestinal inflammation is not sufficient. Mild courses can be treated with topical corticosteroids, while more aggressive disease requires systemic steroids, immunosuppressive agents or anti-TNF. Possible therapeutic

algorithms based on the above presented literature and the joint experience of the authors are shown in online supplementary figure 1 (musculoskeletal EIMs), online supplementary figure 2 (cutaneous EIMs) and online supplementary figure 3 (uveitis).

Multidisciplinary team (MDT) approach

In recent years, it has been increasingly recognised that an MDT approach is needed in IBD care. The complex nature of the disease, the presence of both intestinal and extraintestinal complications and the impact on quality of life are best dealt within dedicated IBD centres.[84 85] Indeed, quality of care has been shown to be superior in specialised IBD centres compared with non-specialist general gastroenterology clinics.[86] The UK IBD standard group recommends scheduled weekly MDT meetings to discuss complex IBD cases. Given the complex nature of EIM and the overlap with various non-GI specialties, an MDT approach with the additional inclusion of ophthalmologists, rheumatologists, dermatologists (depending on the present EIM) is crucial.[10]

FUTURE PERSPECTIVES

The diverse mechanisms underlying and perpetuating inflammation in EIMs are poorly defined, which limits the development of specific treatment strategies. Proposed pathophysiological mechanisms can be broken down into two main hypotheses: (1) EIMs as an extension of immune responses from the gut (due to molecular mimicry, T-cell trafficking and ectopic expression of gut-specific chemokines) and (2) EIMs as an independent inflammatory event (with systemic changes in innate immunity, changes in the microbiome and a general shift toward a proinflammatory state). The lack of specific animal models limits more mechanistic studies. However, newer technologies such as single-cell RNA sequencing may help to characterise the EIM inflammatory process in more detail.

Post hoc analyses of the randomised controlled trials with JAK inhibitors and ustekinumab will help to establish their role in EIM management. However, as for anti-TNF, proper and binding outcomes to assess EIM response are still lacking. Prospective IBD trials usually do not include systematic assessment of EIMs such as performed in rheumatology, dermatology or ophthalmology studies. Binding recommendations on how to assess EIMs and response to treatment have yet to be discussed. Given emerging evidence for the efficacy of anti-TNFs and the potential of newer treatment modalities, comparative trials are needed to define best therapeutic strategies, when EIMs are present. In addition, several open questions remain: should early use of biologics be recommended in the context of an IBD-related EIM? Are combination therapies superior for EIM treatment? And can drug target levels for IBD management be applied one to one for the treatment of EIMs?

CONCLUSIONS

The introduction of anti-TNF therapy has dramatically changed the management of EIMs over the last 10 years. Anti-TNF agents appear to be efficacious for most EIMs, although evidence for their efficacy mostly emerges from non-randomised controlled trials or is extrapolated from studies in rheumatology or dermatology. Despite their beneficial effects, anti-TNFs can also cause anti-TNF-induced skin lesions and therefore

contribute to the burden of EIMs. Anti-integrins might have positive effects on joint and cutaneous manifestations, although underlying mechanisms remain unclear. Data for the use of JAK-inhibitors and anti-IL-12/23 in IBD-associated EIMs are currently limited, but their successful use in rheumatology and dermatology makes a response to these agents reasonable to predict (tables 2 and 3). The use of biological agents that are not approved for IBD cannot be recommended in treatment of EIMs given their possible deleterious effects on intestinal disease itself such as seen for anti-IL-6 and anti-IL-17.

Randomised controlled trials for the treatment of IBD-associated EIMs where activity of EIMs is properly assessed are urgently needed to establish clear and binding guidelines. Simple extraction of EIMs from index scores such as the CDAI in post hoc analyses are not satisfactory to sufficiently evaluate a drug's potential in EIM management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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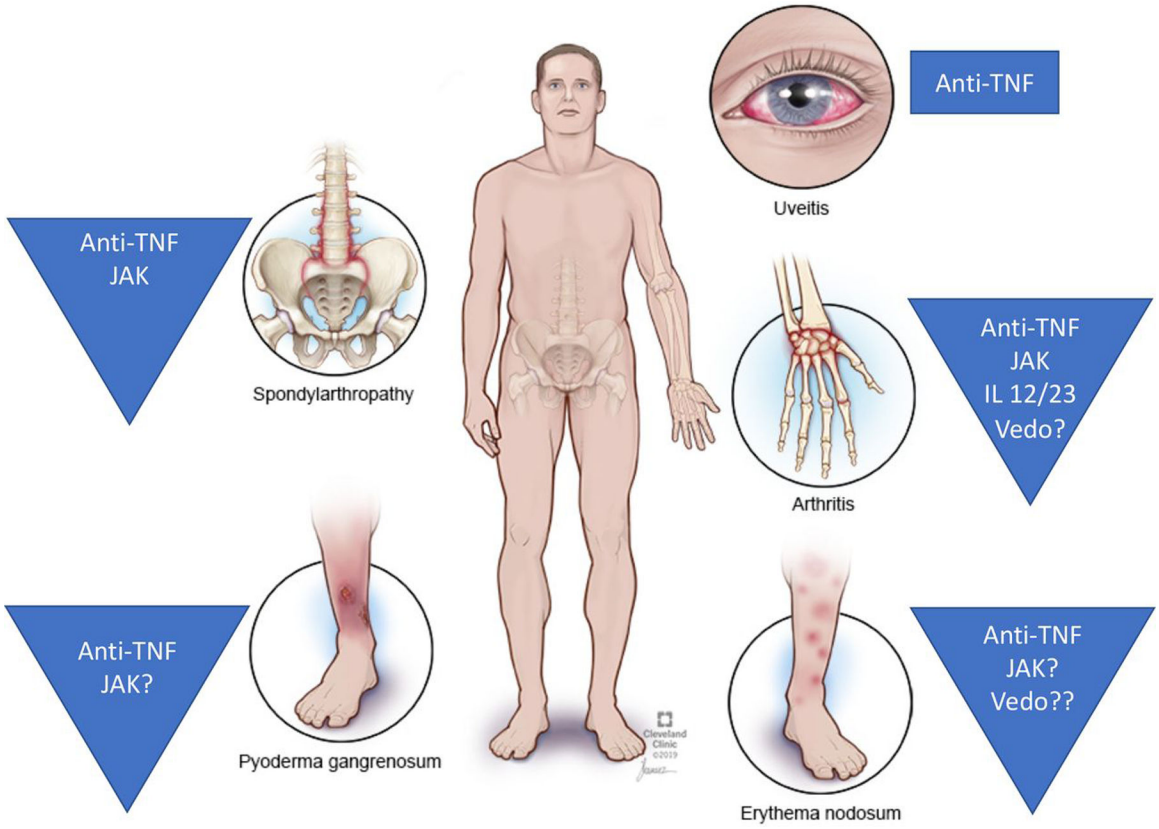

Figure 1.

Overview of the most common EIM and their biological, small-molecule treatment options. EIM, extraintestinal manifestation; IL, interleukin; JAK, Januskinase; TNF, tumour necrosis factor; Vedo, vedolizumab.

Table 1

Synopsis over current and emerging treatment options for different types of EIM

	Conventional treatment	Anti-TNF	Anti-integrins	JAK inhibitors	Anti-IL-12/23	Comments
Axial SpA	Short-term NSAIDs (COX-2)	Early use, particularly in refractory cases	No clinical data available	Efficacious in SpA, not approved yet	Efficacious in phase II trials, phase III trials early terminated	
Peripheral arthritis	Short-term NSAIDs, (COX-2), sulfasalazine MTX	For resistant cases	Response in up to 50%, but also paradoxical arthritis possible	Approved for rheumatoid arthritis	Approved for psoriatic arthritis	Main goal: treatment of underlying IBD
Uveitis episcleritis	Steroids, immunosuppressants	Very efficacious, but small sample size	No data available	Successful use in two patients	Successful use in one patient	
EN	Steroids	Consider in severe or refractory cases	Resolution or partial response, but only case reports/series absence of MAdCAM1 expression in the skin	Approved for psoriatic arthritis, STAT3 expression in skin biopsies of patients with EN	Approved for psoriasis, high improvement rates based on a single case series	Main goal: treatment of underlying IBD
PG	Systemic steroids, CNI (local or systemic)	Consider early use	No resolution with VDZ (case report), absence of MAdCAM1 expression in the skin	Approved for psoriatic arthritis, resolution of PG in three patients	Approved for psoriasis, high improvement rates based on a single case series	

CNI, calcineurin inhibitor; EIM, extraintestinal manifestation; EN, erythema nodosum; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PG, pyoderma gangrenosum; SpA, axial spondyloarthropathy; TNF, tumour necrosis factor; VDZ, vedolizumab.

Table 2

Summary of biologics in IBD and their role in the treatment of IBD-associated EIM. Non-biological treatment options are not shown

	Anti-TNF				Anti-integrins		JAK	IL-12/23
	IFX	ADA	CZP	Goli	VDZ	Natalizumab	Tofa	Ustekinumab
Arthritis								
SpA								
EN								
PG								
Uveitis								

Should be considered.

May be considered.

Cannot be recommended.

ADA, adalimumab; CZP, certolizumab; EN, erythema nodosum; Goli, golimumab; IFX, infliximab; IL, interleukin; JAK, Janus kinase; PG, pyoderma gangrenosum; SpA, axial spondyloarthropathy; TNF, tumour necrosis factor; Tofa, tofacitinib; VDZ, vedolizumab.

Table 3

Current non-IBD FDA-approved indications for biological agents used in IBD management

Biologics	Agent	Approved for the following non-IBD IMIDs
Anti-TNF	Infliximab	RA, SpA, PsA, Pso
	Adalimumab	RA, JIA, PsA, SpA, hidradenitis suppurativa, Pso, uveitis
	Certolizumab pegol	RA, PsA, SpA, Pso
	Golimumab	RA, PsA, SpA
Anti-integrin	Vedolizumab	None
	Natalizumab	Multiple sclerosis
JAK inhibitors	Tofacitinib	RA, PsA
IL-12/23	Ustekinumab	Pso, PsA

FDA, Food and Drug Administration; IL, interleukin; IMIDs, immune-mediated inflammatory diseases; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; Pso, psoriasis; RA, rheumatoid arthritis; SpA, axial spondyloarthropathy; TNF, tumour necrosis factor.