Review

Reactive arthritis: current treatment challenges and future perspectives

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ABSTRACT

Reactive arthritis is a group of inflammatory joint diseases triggered by a previous infection, often associated with extra-articular features. The clinical course and consequently the treatment are complicated by the variability of the disease evolution in the single patient. In some patients, the disease assumes a chronic and destructive course, requiring the introduction of therapy. However, the role of antibiotic treatment of the triggering infection as well as the role of the currently available disease-modifying anti-rheumatic drugs is still unclear. The better understanding of the infectious agents-host interaction in reactive arthritis pathogenesis opens up to the possibility of new therapeutic strategies for the disease management. The purpose of this review is to illustrate the recent discoveries regarding the induction of joint inflammation by the infectious agents, the prognostic factors to better identify patients at risk of chronicity, the current available therapeutic strategies and lastly, the future possibilities of therapeutic approaches to reactive arthritis.

Introduction

Among the inflammatory joint diseases, reactive arthritis (ReA) represents a prototype of infection-induced autoimmunity. ReA is any arthritis triggered by an extra-articular infection in the absence of microorganisms in the synovial fluid of the involved joints. The disease was first described in 1916 as a part of a triad of arthritis, non-gonococcal urethritis, and conjunctivitis. Thereafter, many pathogens have been identified as causative microorganisms. So far, no diagnostic or classification criteria have been established for ReA. The American College of Rheumatology (ACR) released general guidelines, which include rheumatological signs along with a proof of infection (1).

Depending on the anatomical site of infection, ReA can be divided into uro-arthritis and entero-arthritis. The most common agent triggering ReA after a genitourinary infection is *Chlamydia trachomatis,* whereas *Shigella, Salmonella, Yersinia and Campylobacter* are the most common involved agents in gastroenteric-associated disease. The classical ReA belongs to the spectrum of the spondyloarthritis (SpA), a group of diseases that includes ankylosing spondylitis (AS) psoriatic arthritis (PsA) and, arthritis associated with inflammatory bowel diseases (IBD). This group of diseases shares many features such as association with HLA-B27 – carried by 30–80% of patients in population studies – absence of rheumatoid factor, tendency towards a family aggregation, common musculoskeletal manifestations including sacroiliitis, enthesopathy, asymmetrical oligoarthritis predominantly of the lower limbs, and typical extra-articular features: urethritis, iritis, conjunctivitis and mucocutaneous lesions (balanitis, keratoderma blenorrhagicum). Besides the most common pathogens, many other infectious agents have been associated with non-classical ReA, such as *Borrelia, Brucella, Haemophilus, Leptospira, Mycobacteria, Neisseria, Staphylococcus, Streptococcus, Ureaplasma, BCG and Vibrio spp* (2). These non-classical ReA cannot be included in the SpA spectrum since they are not associated with HLA-B27 and exhibit distinct clinical features such as a predominant peripheral and polyarticular arthritis (3).

Methods

The aims of this review were: 1. to gather the most recent evidences about pathogenetic mechanisms of ReA and

the natural history of the disease; 2. to identify the prognostic factors that emerged from population studies; 3. to summarise the current therapeutic strategies for ReA manifestations; 4. to present the results of antibiotic treatment in ReA; 5. to speculate about possible future treatment strategies, taking into account the new pathogenetic insight and the results of biologic treatment in ReA. Thus, a literature search was made in PubMed, accessed via the National Library of Medicine PubMed interface (http://www.ncbi.nlm.nih.gov/pubmed). Firstly, PubMed was searched using the term "reactive arthritis" OR "post-infectious arthritis" in combination with (AND) "Chlamydia" OR "infections" OR "Enteric pathogens". Secondly, the same PubMed research was combined with other terms, such as "pathogenesis" OR "prognosis" OR "Salmonella" OR "Shigella" OR "Yersinia" OR "Campylobacter" OR "Escherichia" OR "DMARDs" OR "biologic" OR "treatment" OR "antibiotic". A total of 13,793 articles were obtained: we excluded all the articles not focusing on reactive arthritis or post-infectious arthritis. After a stringent selection, in the present review we evaluated 17 papers concerning pathogenetic mechanisms of reactive arthritis, 21 concerning long-term follow-up and prognosis and finally, 43 on the treatment of reactive arthritis, including 8 papers on biologic treatment and 15 papers concerning antibiotic treatment. Further relevant data were obtained from the reference lists of articles returned using these search terms and from the authors' own experience and knowledge of the literature.

Pathogenesis

The current evidence suggests that after the initial enteric or urogenital mucosal infection, bacterial antigens or even viable microorganisms reach the joints trough the bloodstream, where they act as pathogen-associated molecular patterns (PAMPs) activating the immune system. In *Chlamydia*-induced arthritis, bacteria-infected monocytes/macrophages act as carriers of viable microorganisms from the infection site to the articular space; once in the joint, *Chlamydia* persists in an unusual form, morphologically aberrant but viable and metabolically active. Traditional cultural techniques are not able to identify the pathogen while electron microscopy, immunofluorescence and PCR can detect it in synovial samples of involved joints. The persistence of *Chlamydia* determines inflammation inducing a predominant Th1 response and production of pro-inflammatory mediators, such as tumour necrosis factor-α (TNF-α), interleukin-1 and interferon-γ (IFN-γ) (4). In post-enteric ReA, no viable bacteria but only their products have been demonstrated in synovial tissue or fluids of affected patients. Intracellular bacteria can survive for more than 2 weeks in cultures of synovial fibroblasts infected with *Salmonella* and *Yersiniae*, then the microorganisms are slowly and progressively degraded by host cells leading to the formation of so-called "bacterial ghosts"; these bacterial remnants are only composed of lipopolysaccharide (LPS)-containing bacterial wall, without DNA and no viability. The ability of the bacterial wall to persist for a long time in synovial cells suggests that this structure may contribute to synovial inflammation by releasing arthritogenic molecules (5). In general, the pathogens involved in post-enteric ReA are Gram-negative bacteria endowed with a bacterial wall characterised by the Outer Membran Proteins (OMPs). These virulence factors are fundamental for bacterial adhesion, entry, survival in macrophages and for eukaryotic cell invasion. OMPs are mainly composed by LPS, lipoproteins and porins. Recently, a proteomic analysis revealed that some proteins from *Salmonella*'s OMPs are the immunodominant antigens that stimulate T cells in patients with *Salmonella*-induced ReA (6). After enteric yersiniosis, *Yersinia* antigens persist in the blood and in the joint for a long time after the infection resolution, both in patients who developed ReA and in subjects with uncomplicated infections (7). Some authors recently demonstrated that in *Y. pseudotuberculosis*-infected mouse models, the cecum is the site of persistent infection and bacteria can be detected by immunofluorescence in close proximity to caecal lymphoid aggregates. The increased serum levels of cytokines such as IL-1β, IL-4, IL-17, and TNF-α suggests a complex host response to bacteria antigens, involving Th1, Th2 and Th17 lymphocytes. From the primary site of infections, circulating antigens probably reach the joints where they may trigger a systemic immune response (8). Figure 1 summarises the possible physiopathology of ReA.

Clinical manifestations, natural history and prognosis

Clinical manifestation and diagnostic criteria

Several clinical rheumatologic manifestations, such as arthritis, enthesitis, spondyloarthritis and dactylitis, belong to the spectrum of ReA. ReA usually manifests as a monoarthritis or an asymmetric oligoarthritis involving mostly lower extremities, emerging days to weeks after the triggering infection. Large joints are usually involved but involvement of the small joints of the hands is not uncommon. Enthesitis of the lower extremities, in the form of a plantar fasciitis or an Achille's tendon enthesitis, is common at presentation and should raise the suspicion of a ReA. Axial skeleton involvement, usually a sacroiliitis or less frequently a cervical and thoracic spine involvement, is also common and is usually seen in patients HLA-B27 positive. Dactylitis or rather the inflammation of the entire digital soft tissues, may manifest in up to 40% of patients (9). Extra-articular features are also common. Ocular involvement, in the form of conjunctivitis or anterior uveitis, manifests in 50–75% of patients, even early in the course of the disease. Especially in patients HLA-B27 positive, uveitis may develop a chronic or relapsing course, with potential sight-threatening consequences. Other eye involvement by ReA such as retinal vasculitis, scleritis, corneal ulcerations and optic neuritis have been less commonly reported (10). Dermatologic manifestations of ReA are characteristic, and develop in up to 40% of patients. Balanitis circinata is the most common skin manifestation and is characterised by the development of serpiginous and annular erythematous lesions of the glands.

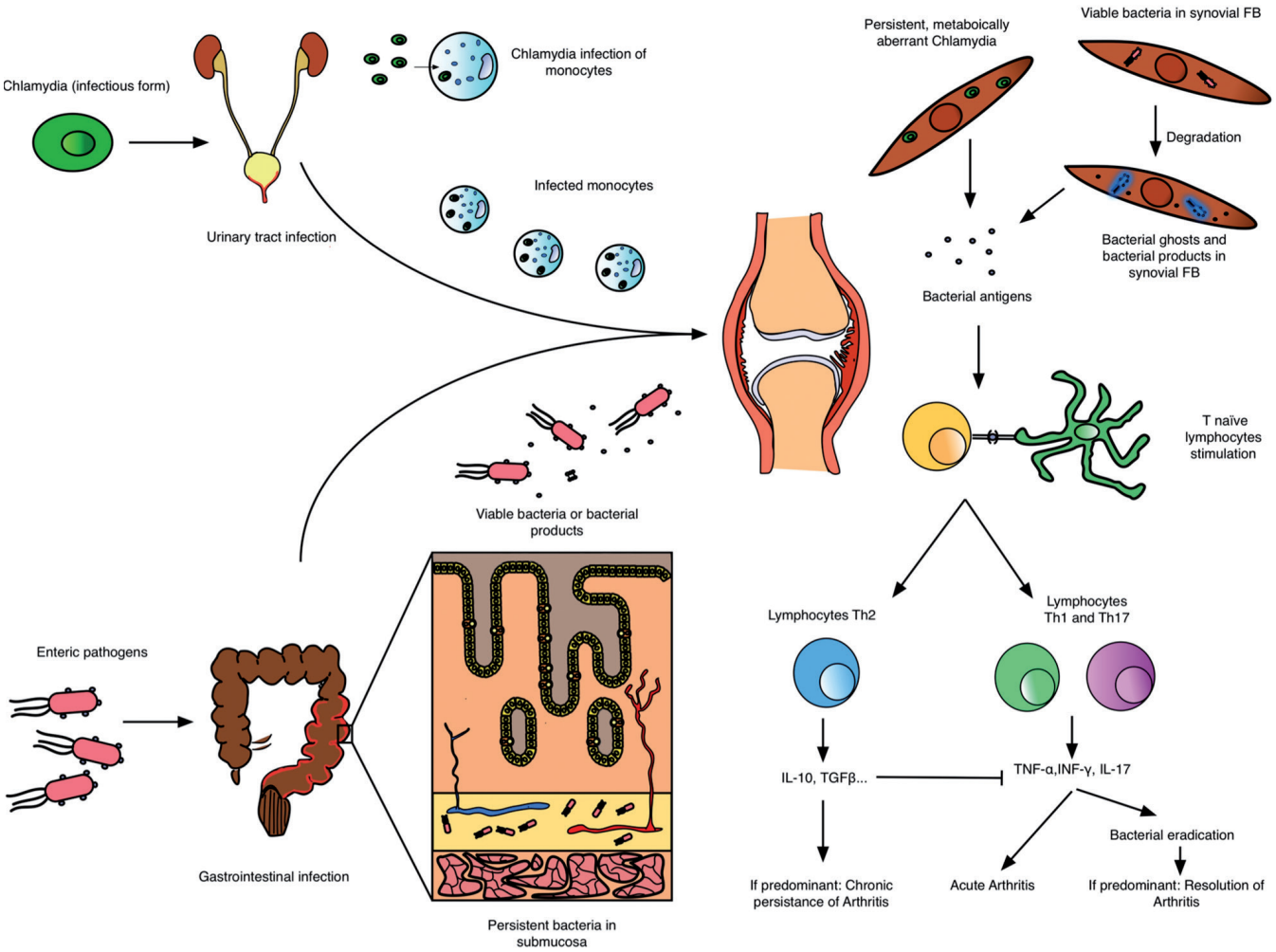

Fig. 1. Hypothesised pathogenesis of ReA.
In Chlamydia-induced ReA, urinary tract infection represents the site of entrance of the pathogens. Chlamydia is able to sustain an intracellular infection of monocytes. In enteric-triggered ReA, enteric pathogens cause an acute infection of the gastrointestinal tract. The bacteria show the ability to persist in the submucosal layer of the bowel. Via bloodstream, viable bacteria or bacterial products released by the intestinal wall, as well as Chlamydia-infected monocytes can reach the joints. Chlamydia can sustain a chronic infection of synovial fibroblasts in a persistent and metabolically aberrant but viable form. Enteric pathogens can show viability in the extremely early phases of the disease, but are quickly degraded by synovial fibroblast, leading to the formation of bacterial ghosts and other bacterial products that can persist in the intracellular space of synovial fibroblasts. These possible mechanisms of bacterial persistence inside the joints represent the source of antigens that can stimulate the activation of T lymphocytes. The development of a predominant Th1 and Th17 response, through the production of cytokines like TNF-α, can mediate the eradication of bacterial products from the joint, leading to the resolution of the disease. On the contrary, a predominant Th2 response, through the production of cytokines like IL-10, can suppress the development of an effective Th1 and Th17 response and the subsequent bacterial eradication, leading to the chronicity of the arthritis. Periodic imbalance between Th2/Th1-Th17 cytokines, with a temporary increase in Th1-Th17 cytokine production during the chronic course of ReA are responsible for acute relapses of the arthritis.
FB: fibroblast; Th1: T helper 1; Th2: T helper 2; Th17: T helper 17, IL-10: interleukin 10; TGF-β: transforming growth factor β; TNF-α: tumour necrosis factor α; IL-17: interleukin 17.

Around 10% of patients may also develop a palmo-plantar psoriasiform rash called Keratoderma blenorrhagicum. Mouth ulcerations are found in a minority of patients. Cardiac manifestations, including aortitis and aortic valve insufficiency, myocarditis, pericarditis and conduction disturbances, may develop in up to 10% of patients. Valvular disease and heart block may develop early during the disease, while pericarditis, on the contrary, tends to manifest in patients with a long illness duration (1-3, 9).

To date, there is still no univocal and validated set of criteria to support the diagnosis of ReA, mainly for the broad spectrum of clinical manifestations and the difficulties in defining the causal relationship with the triggering infection (11). The widest used set of criteria was developed during the Third International Workshop on Reactive Arthritis in Berlin. According to this, ReA is defined as an asymmetrical oligoarthritis predominantly of the lower limbs, with evidence of preceding infection (clinical diarrhoea or urethritis within the preceding 4 weeks, positive stool cultures, detection of *C. trachomatis* in urine or in a urogenital swab, positive serology to *Yersinia, Salmonella. or C. trachomatis*, or detection of chlamydial DNA in the joint by PCR) and exclusion of patients with other known causes of oligoarthritis (12). The new insights into the pathogenesis of ReA would hopefully allow the development of updated and reliable criteria, useful in a clinical setting.

Natural history and prognostic factors

ReA usually has a good prognosis, with a self-limiting course and full recovery in 3 to 5 months. However, a variable number of patients may develop a chronic disease, defined by the persistence of clinical symptoms for more than 6 months. Subjective arthralgia without evidence of joint damage and low back pain are frequently reported after ReA. The onset of an inflammatory spine disease after the ReA has also been described, with an overall incidence of about 15% for AS and about 30% for radiological sacroiliitis. Recurrent episodes of arthritis, sometimes progressing to chronic deforming arthritis with evident joint erosions, enthesitis and recurrent iritis can occur. It is mandatory to identify patients with a poorer prognosis who develop chronic or recurrent articular or extra-articular features of the disease, so as to promptly diagnose and treat these potentially debilitating manifestations. Prognostic factors predicting long-term outcomes include specific infections, presence of HLA-B27, positive family history for SpA or AS, and presence of chronic gut inflammation (13). Data on long-term prognosis are available mainly for enteric-triggered ReA, depending on the causative pathogen. In a Finnish study evaluating the natural course of 50 patients with *Salmonella*-induced ReA, with a mean follow-up of 11 years, up to 60% of the patients had residual symptoms during the follow-up: 44% complained of chronic inflammatory back pain and 20% inflammatory arthralgia. In eight patients (16%) the diagnosis of chronic spondiloarthritis was made (14). Similar studies on *Yersinia*-triggered ReA reported a full recovery in about 20–50% of patients, whereas up to half of patients reported mild peripheral joints symptoms, and 37% of patients had persistent low back pain. About 10–15% of patients developed AS and about 10–30% developed radiological sacroiliitis during follow-up (15, 16). The same outcome has been reported for *Shigella*-induced ReA (17). The reported incidence of *Campylobacter*-induced ReA after an acute infection ranges from 5% to 16%, and about 0–7% to 24% of patients subsequently develop chronic symptoms including arthralgia and clinically manifest arthritis (18). In a cohort of 86 patients exposed to *Campylobacter*, Bremmel *et al*. reported an incidence of 5% of chronic or relapsing rheumatic conditions (19). In another study on 27 patients with *Campylobacter*-induced ReA, 5 were symptomatic for more than 1 year (20). Overall, the prognosis of enteroarthritis seems to be better than that of *Chlamydia*-induced ReA. Among patients with *Chlamydia*-induced ReA, 17% developed a chronic disease (21). In long-term (10 to 20 years) follow-up series of *Chlamydia*-induced ReA, up to 68% of patients persistently complain of arthralgia, about 50% developed radiologically evident sacroiliitis and about 25% were diagnosed as AS. Patients with *Chlamydia*-induced ReA are also at a higher risk to developing a relapsing course of arthritis. HLA-B27 positivity is a strong negative prognostic factor. Overall, the frequency of HLA-B27 among ReA patients ranges from 30% to 80%, and HLA-B27 carriers are more likely affected by severe disease, with frequent spine involvement, extra-articular features and a chronic course of arthritis (22). In enteric-triggered ReA, HLA-B27 positivity determines the clinical evolution and disease outcome, according to the microorganism responsible. In a cohort of patients with *Salmonella* infection and musculoskeletal symptoms, 75% of HLA-B27 positive patients developed ReA (23). In the original baseline cohort of patients with *Salmonella*-induced ReA descripted by Leirisalo *et al*., 88% of patients were HLA-B27 positive: only those patients developed recurrent arthritis, acute iritis and radiological sacroiliitis (14). In a ten-year follow-up study, patients with *Yersinia* infection and acute ReA carrying the HLA-B27 allele tended to develop more frequently low back pain and radiological evidence of sacroiliitis (24). Similar results have been described in *Campylobacter* and *Shigella* associated ReA, with a more severe disease course in HLA-B27 positive patients (25-27). More recently, the HLA-B27 prevalence among ReA patients was downscaled to about 30–50%; therefore, HLA-B27 seems to be a prognostic marker of a more severe disease course rather than a susceptibility marker (28). Indeed, HLA-B27 positive patients who develop ReA are more likely to present extra-articular features such as urethritis, mucocutaneous lesions (circinate balanitis, keratoderma blennorrhagicum, and nail dystrophy), cardiac and neurological involvement, amyloidosis, thrombophlebitis, pleuritis, and ocular involvement. Anterior uveitis is a severe manifestation of ReA, second to conjunctivitis in frequency, affecting about 12% of patients with ReA. Patients with HLA-B27 positive sacroiliitis more frequently develop uveitis, which can have a relapsing course. Overall, patients who manifest the classical triad arthritis, urethritis and conjunctivitis, have a poorer prognosis (29). As in other SpA, male gender is a negative prognostic factor in patients with ReA. In a Finnish cohort followed up for 20 years, males were more prone to develop sacroiliitis and to progress to AS compared to women. Recurrent episodes of acute ReA, more frequently detectable in *Chlamydia*-induced ReA, and family history of SpA were other factors associated with the evolution of a chronic course (12, 30).

Recent evidence is pointing to the role of microscopic gut inflammation in the pathogenesis and natural history of reactive SpA. About half of SpA patients have microscopic gut inflammation paralleling the joint inflammations: when arthritis is in remission, also the gut inflammation attenuates and *vice versa*. The first endoscopic studies on SpA patients demonstrated a prevalence of subclinical gut inflammation in about 20% of uroarthritis and 90% of enteroarthritis. In patients with persistent joint inflammation, the repetition of the endoscopy showed a strong association with a persistent gut inflammation (31). More recently, the results from the Ghent Inflammatory Arthritis and spoNdylitis cohorT (GIANT) confirmed the high prevalence of microscopic gut inflammation in SpA (about 45% of patients), and the association with a trend to progress to axial manifestation of AS among patients who present persistent inflamma-

tion (32). In ReA, the prognostic value of persistent gut inflammation has been documented in *Yersinia* infection. As previously reported, *Yersinia* can persist in bowel submucosa for a long period, determining a prolonged release of bacterial antigens and a chronic systemic inflammatory response (33). Persistent infection is an ability also pertaining to *Chlamydia,* which could explain the tendency toward acute relapse and chronic evolution. In this light, the eradication of persistent *Chlamydia* infection offers the opportunity of a cure, as demonstrated in two recent clinical trials showing the effectiveness of antibiotic combination therapy (34).

Treatment

General goals of ReA treatment are
1. to promptly identify – and, if necessary, to treat – the triggering infection,
2. to assure symptomatic relief,
3. to minimise disability in chronic disease.

Antibiotic treatment of triggering infections

Current evidence suggests that early treatment of the triggering infection could prevent the initiation and the persistence of the subsequent arthritis, at least for uroarthritis, by reducing the spreading of bacteria and/or bacterial antigens to the joints. In a retrospective study on 109 patients treated for genitourinary infections with antibiotic therapy against *C. trachomatis*, the risk of a subsequent arthritis was reduced from 37% to 10% (35). Currently, a non-gonococcal genitourinary infection needs to be treated with azithromycin 1 gr in a single administration or doxycycline 100 mg twice a day for 7 days, regardless of the presence of arthritis. Sexual partners should be treated simultaneously, and patients should be advised about the risk of relapse in case of re-infection and about specific preventive measure to avoid it (36). In patients with acute Chlamydia-induced ReA, the high prevalence of re-infections within the first 3 months suggests a longer antibiotic course (4 to 12 weeks) either with doxycycline or ciprofloxacin (37). The evidence for a role of antibiotic treatment in post-enteritic ReA is weaker. In a Swedish study on an outbreak of *S. Enterica* infection among 126 medical practitioners, early antibiotic treatment did not prevent the development of ReA and did not affect the disease course (38). Similar results were obtained from a randomised prospective trial on 40 patients with post-enteritic ReA triggered by *Salmonella, Yersinia* and *Campylobacter*: 10–14 days of antibiotic course failed to ameliorate clinical symptoms, arthritis duration and serum markers of inflammation (39). These findings suggest that in post-enteritic ReA, the pathogenic events leading to the development of the arthritis – which could be the bacterial antigen spreading from bowel to joints – occur very early in the course of the infection, so that the introduction of antibiotic therapy may take place too late to influence the disease course. In contrast with previous data, a recent study reported that early antimicrobal treatment for salmonellosis, with an average of 10 days from the onset of diarrhoea, reduced the incidence of acute musculoskeletal symptoms. However, there was no distinct interval of time within early treatment that would have prevented the development of musculoskeletal symptoms and the size of the study was too small to draw definitive conclusions (40). To date, in enteric-triggered ReA there is no indication of short-term antibiotic treatment. On the contrary, short-term antibiotic course may be considered in the case of severe diarrhoea, immunocompromised or elderly patients, or to prevent a possible relapse in patients with a previous history of ReA (13, 41).

Management of acute arthritis

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line therapy in acute ReA. This class of drugs has a proven efficacy in treatment of clinical manifestations of SpA – inflammatory back pain, peripheral arthritis or enthesitis (42-44). In ReA, the efficacy of NSAIDs was tested in few clinical trials and no single molecule proved to be more effective than the others (45, 46). Clinical manifestations and safety profile should drive the choice of the molecule. In patients with prevalent inflammatory back pain, drugs with long half-life such as naproxen are preferred, whereas in patients at high risk for gastric bleeding, a COX-2 selective inhibitor seems a reasonable option. In the view of the frequently self-limiting course of ReA, NSAIDs can be the only pharmacologic intervention in the acute phase. The individual response to the different drugs suggests trying several NSAIDs for at least 2–4 weeks at full dose before shifting to another one (47). Once identified, the effective agent should be administered at a proper dose in a continuative manner for weeks or months, to assure prolonged relief of symptoms and to allow patients to be physically active (37). Treatment with glucocorticoids (GCs) should be considered in the case of inadequate response to NSAIDs or persistent active disease for more than 4 weeks. In the case of mono or oligoarticular involvement, bursitis, enthesopathy, tenosynovitis or other local manifestations of the disease, GC infiltration assures a good symptomatic response (36, 47, 48). In the case of polyarthritis, high active disease, inadequate response to NSAIDs and to intraarticular glucocorticoids, or severe extra-articular manifestations, systemic GCs should be considered (21). A short course – up to 4 months of GCs, starting with 20–40 mg daily of prednisone then tapered to the lowest dose, should be used to control symptoms. Often the response to systemic GCs is lower than in other forms of arthritis such as rheumatoid arthritis, and there is no evidence of any benefit of prolonged treatment in ReA. Systemic GCs can also be used for the management of acute peripheral relapses of the disease (33, 49). On the contrary, GCs have only limited value, if any, in axial manifestations of ReA. Consequently, they should not be used in this subset of the disease (37). Non-pharmacologic treatment, such as physical therapy and orthoses are essential tools to maintain mobility and to limit pain, and should be tailored according to the patient's needs (46).

Chronic arthritis management: conventional synthetic DMARDs

In patients who develop chronic arthritis or with acute arthritis resistant to

therapy with NSAIDs and GCs, treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) is usually indicated. Given the good prognosis of ReA, with a complete resolution of clinical manifestations in up to 6 months, a careful period of observation of 3–6 months before starting a DMARD is often recommended, to avoid potential overtreatment of patients with a self-limiting disease. On the other hand, chronic ReA may determine an erosive disease with subsequent joint deformity, thus DMARD treatment could be advisable (49-50). The evidences on DMARD use in ReA are scant (51). Sulphasalazine (SSZ) is the most extensively studied csDMARD in ReA. Sulphasalazine inhibits NF-κB activation in LPS and TNF-α stimulated cells (52, 53). Furthermore, SSZ seems to be able to normalise intestinal permeability and possibly prevent enteric antigen dissemination (54). The efficacy of SSZ in ReA has been demonstrated in a large multicentre double-blinded clinical trial on 134 patients with chronic ReA who were unresponsive to NSAIDs, and were randomised to receive SSZ 2000 mg daily or placebo. A significant higher response rate was observed in the SSZ group (62.3% *vs*. 47.7%) (55). It should be underlined that SSZ was effective only in patients with peripheral arthritis, without any significant effect on axial disease. Considering its effectiveness in inflammatory bowel disease, SSZ could be a good option especially in patients with post-enteritic ReA and in patients with endoscopic signs of intestinal inflammation (50, 54). SSZ treatment can be started at the dose of 500 mg daily and progressively increased to 1000 mg twice a day, up to a maximum daily dose of 3000 mg, monitoring patients for possible adverse events. There is less evidence for other csDMARDs in ReA treatment. Methotrexate (MTX), administered parenterally once a week, has been used in patients with refractory ReA with good results on peripheral arthritis and dermatological manifestations (56). MTX may be used in patients who are intolerant or refractory to SSZ treatment, at the same doses and schedule (7.5 to 25 mg weekly) as used in rheumatoid arthritis or psoriatic arthritis, as an alternative or in combination with SSZ (49). Only one study evaluated the efficacy of azathioprine in ReA, reporting a good response at the dose of 1–2 mg/kg body weight daily. However, due to the small sample size, no final conclusion can be drawn (57).

The same considerations can be made for cyclosporine A. There are some anecdotal reports of its efficacy, but no clinical trial has been conducted and its role in ReA treatment has not been established yet (58, 59).

Chronic arthritis management: biologic DMARDs

The availability of several inhibitors of TNF-α has revolutionised the treatment of many inflammatory arthritis. TNF-α inhibitors demonstrated quite impressive results in the treatment of axial and peripheral manifestations of ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease-associated spondyloarthritis (60), but only few data are available on the role of TNF-α inhibitor treatment in ReA. Table I summarises the available studies on TNF-α inhibitors in ReA. Only small case series and case reports have been published. Anecdotal evidences of anti-TNF use in ReA, especially infliximab, come from case reports describing a good response independently of the triggering infection or the microbiological identification of the pathogen. The largest patient series available has been reported by Flagg *et al*., who conducted an open-label trial involving 16 patients with undifferentiated or reactive arthritis treated for 6 months with etanercept 25 mg subcutaneous twice a week. Ot the 10 patients who completed the study, 9 were classified as responders to etanercept. Synovial biopsy and PCR analysis for bacterial nucleic acid were performed before and after etanercept therapy in 6 patients, all classified as responders. Of 3 patients who initially showed positivity for *C. Trachomatis* 16S rRNA to PCR analysis, 2 had negative PCR results after treatment. On the contrary, two patients initially negative for *Chlamydia* rRNA at PCR analysis became positive during the treatment. Furthermore, there was a histological improvement in 5 out of 6 patients on examination of the synovial specimens although with no complete normalisation of the histology (61). The role of bacterial load in the joint affected by ReA, and the possible effect of TNF inhibitors on bacterial proliferation in synovial tissues has not been formally evaluated to date, but there is some evidence of good responses despite an increased bacterial load in joints of patients treated with TNF inhibitors (62).

Currently, the role of TNF-α in the pathogenesis of ReA and in the bacterial eradication from synovial tissue has not been fully understood. The serum level of TNF-α is higher in ReA patients than in normal controls, even though this cytokine is expressed at lower levels when compared with other forms of inflammatory arthritis (63, 64).

Bacterial eradication from synovial tissues may be influenced by the TNF-α production: TNF-α is produced early in the synovial tissue of ReA patients and it can inhibit the growth of many intracellular bacteria classically associated with ReA induction, so it may play a role in bacterial eradication from the joints (65-67). Nevertheless, ReA patients show a predominant Th2-polarised response with a lesser production of Th1 cytokines such as TNF-α and IFNγ compared to Th2 cytokines such as IL-10; Th2 cytokines can prevent an effective Th1 response, limiting bacterial eradication and contributing to ReA pathogenesis (67). Patients with chronic ReA present lower levels of TNF-α compared with patients with a self-limiting disease, and *in vitro* studies have shown that lower levels of TNF-α in human cells exposed to *Chlamydia*, in synergy with a reduction of IFNα levels, are associated to persistent aberrant chlamydial infection (68, 69). These evidences have raised concerns about a possible negative effect of TNF inhibition in ReA patients, through the promotion of the persistence or the dissemination of microbial agents in the joints, leading to a possible worsening the disease. A recent work revealed severe features of *Yersinia*-triggered ReA in a mouse model that lacked

Table I. Biologic agents in ReA.

Authors (year)	n. of patients	Clinical manifestations or inclusion criteria	Microbial agent identified	Biologic	Results
Kaipiainen-Seppänen (2003)	2	Peripheral synovitis after a documented enteric infection	*Yersinia*	IFX	Good response
Gill (2008)	1	Asymmetric oligoarthritis and keratoderma blenorrhagicum developed after an episode of urethritis, refractory to NSAID and MTX	None	IFX	Complete remission
Wechalekar (2010)	1	Asymmetric oligoarthritis developed after an episode of urethritis, refractory to SSZ, MTX and intraarticular GC	*Chlamydia*	IFX	Complete remission
Schafranski (2009)	1	Asymmetric oligoarthritis of lower limbs developed after an episode of urethritis, refractory to NSAID, SSZ and MTX	*Chlamydia*	IFX	Complete remission
Thomas-Pohl (2012)	1	Acute febrile polyarthritis after an enteric infection, refractory to NSAID and intravenous GC	None	IFX	Complete remission
Abdelmoula (2008)	1	Peripheral synovitis after a an episode of urethritis	None	IFX	Complete remission
Meyer (2011)	10	ReA as defined by the criteria of the Third International Workshop on Reactive Arthritis, failure of conventional drugs, and anti-TNF therapy given within 12 months of the triggering infection.	6 *Chlamydia* 2 Enterobacteria	IFX, ETA, ADA	90% of patients responders (A)
Flagg (2005)	10	Persistent, active inflammatory arthritis of at least 3–4 weeks' duration in at least 1 peripheral joint. Joint fluid aspiration was required to document inflammatory fluid. Clinically observed or laboratory documented urethritis, enteritis or bronchitis within 6 weeks of onset of the arthritis, or PCR evidence of bacterial DNA in the join.	5 *Chlamydia*	ETA	90% of patients responders (B)

Good response: Reduction of overall joint symptoms, back pain and ESR and CRP levels, but persistence of episodes of arthritis.
Complete remission: complete resolution of the clinical manifestation, normalisation of inflammatory markers, no recurrence of the arthritis.
Responders: >30% improvement in pain on the VAS, in the tender joint count, and in the swollen joint count, or >30% improvement in extraarticular manifestations, and a CRP level 20 mg/litre (**A**); 2 of the following 3 assessment measures: at least a 2-point decrease in the 10-point VAS for pain, at least a 30% decrease in tender joint count, and at least a 30% decrease in swollen joint count (**B**).
NSAID: non-steroidal anti-inflammatory drug; MTX: methotrexate; SSZ: sulphasalazine; GC: glucocorticoids; PCR: polymerase chain reaction; IFX: infliximab; ETA: etanercept; ADA: adalimumab.

TNFR p55 signalling. The mice presented higher synovial production of IL-17 and IFNγ that could act synergistically to sustain bacterial-triggered inflammation (70). Nevertheless, available clinical results of ReA patients treated with TNF inhibitors showed a good symptomatic response with no increase in infection rate sustained by the triggering microbial agents. Meyer *et al*. reported a 90% response rate in 10 patients with recent-onset ReA, with no documented adverse event, including severe infections. Only mild infections were documented, none of which were correlated to the triggering microorganism. Nonetheless to date, the overall number of TNF inhibitor treated patients is globally insufficient to clearly excludethe safety issues of these drugs in ReA treatment. TNF-α, together with other cytokines produced in response to persistent bacterial antigens in the joint, may contribute both to bacterial eradication from synovial tissue and to the development of inflammatory manifestations of the disease. Therefore, this contradictory role could explain the clinical improvement despite an increased bacterial load of the microorganism (71). Carter *et al*. reported a series of 3 patients with RA who developed palmoplantar psoriasiform pustular eruption while on TNF inhibitor therapy. All were positive to *C. Trachomatis* at PCR examination, giving rise to the hypothesis of a possible manifestation of keratoderma blenorrhagicum (72). For this reason, caution on TNF inhibitor treatment of ReA patients is advisable, limiting this option to patients refractory to conventional therapy, at least until further studies will definitely exclude safety issues.

Management of extra-articular manifestations

The treatment of the extra-articular manifestations should be individualised on the specific clinical features and should involve other specialists, such as the dermatologist and ophthalmologist. Skin manifestations, such as psoriasiform lesions and circinate balanitis, usually respond well to topical glucocorticoid treatment with or without keratolytic agents. In the case of more severe manifestations, methotrexate or retinoid agents may control the disease manifestations. Mouth ulcerations do not usually need treatment, since they lead to a spontaneous resolution. Anterior uveitis is generally treated under ophthalmologists' advice, with topical glucocorticoids associated to mydriatics. In the case of posterior uveitis, intravitreal administration of glucocorti-

Table II. Antibiotics study design, outcomes measures and results in ReA.

Authors (year)	Study design	n. of patients and diagnosis	Intervention	Assessment and outcome measures	Results
Tetracyclines					
Lauhio (1991)	Double-blind, randomised	40 ReA (21 uroarthritis, 17 enteroarthritis)	Lymecycline for 3 months *vs*. placebo	Clinical and laboratory evaluation at 1, 2, 3 and 6 months; disease activity and time to recovery	In *Chlamydia* ReA treated with lymecycline, reduction of the duration in weeks of arthralgia and elevation of ESR and CRP. Shorter time to recovery
Leirisalo-Repo (2003)	Cohort study, retrospective	17 ReA (9 lymecicline group, 8 placebo group)	10-year follow-up of patients included in the study by Lauhio (1991)	Clinical, laboratory and radiological examination. Past 10 years medical history collection; Progression to a peripheral or axial arthritis	No effect on long-term outcome in term of development of peripheral or axial arthritis
Wollenhaupt (1997)	Double-blind, randomised	32 *Chlamydia* ReA	Doxycycline for 4 weeks *vs*. doxycycline for 4 months	Clinical manifestations, markers of inflammation and remission at the end of the study	No difference between short and long term in term of clinical manifestations, serum markers of inflammation and remission achievement
Putschky (2006)	Double-blind, randomised	32 *Chlamydia* ReA	Doxycycline for 10 days *vs*. Doxycycline for 4 months	Clinical manifestations and laboratory evaluation at the beginning and at the end of the study; Remission at the end of the study	No difference between short- and long-term in terms of clinical manifestations, serum markers of inflammation and remission achievement
Ciprofloxacin					
Sieper (1999)	Double-blind, randomised	55 *Chlamydia, Salmonella* or *Yersinia* ReA, 49 undifferentiated SpA	Ciprofloxacin for 3 months *vs*. placebo	Clinical and laboratory examination after 3 months; Percentage of patients in remission after 3 months of treatment	No clinical advantage (in *Chlamydia* ReA ciprofloxacin better than placebo but no statistical significance)
Toivanien (1993)	Double-blind, randomised	36 Chronic (>6 months) ReA (4 uroarthritis, 32 enteroarthritis)	Ciprofloxacin for 3 months *vs*. placebo	Clinical manifestations and inflammatory markers improvement 6 months after treatment stop.	Decrease of arthralgia and MS in treated patients whereas decrease of Ritchie index and ESR in the control group. No definitive advantage for treatment group.
Yli-Kerttula (2000)	Double-blind, randomised	71 Acute (<3 months) ReA (11 uroarthritis, 60 enteroarthritis)	Ciprofloxacin for 3 months *vs*. placebo	The outcome measures were ESR, number of swollen joints, PGA and complete recovery.	No significant differences in any of the efficacy variables between the study groups at baseline or during the 12-month follow-up.
Yli-Kerttula (2003)	Cohort study, retrospective	53 ReA (26 ciprofloxacin group, 27 placebo group)	4-7 year follow-up of patients included in the study by Yli-Kerttula (2000)	Clinical, laboratory and radiological examination. Past medical history collection; Progression to a peripheral or axial arthritis	Significant higher achievement of complete recovery in the treatment group. Treatment in acute phase may prevent chronic evolution of disease (especially for HLA-B27+ patients)
Gatus (1999)	Double-blind, randomised	56 ReA, 42 Recurrent anterior uveitis, isolate or secondary to ReA	Ciprofloxacin for 12 months *vs*. pbolacebo	Clinical and ophthalmologic assessment after 12 months from the end of the treatment; Time to disease relapse and severity scores evaluation.	No statistically significant difference on the natural history or severity in the treatment group
Hoogkamp-Korstanje (2000)	Double-blind, randomised	18 *Yersinia* ReA	Ciprofloxacin for 3 months *vs*. placebo	Symptoms and inflammatory markers improvement and remission achievement 12 months after treatment	Higher percentage of remission in treatment group. Faster symptoms and inflammatory markers improvement in treatment group
Azithromycin					
Kvien (2004)	Double-blind, randomised	152 Acute (<2 months) ReA	Azithromycin 1 gr single dose followed by Azithromycin 1 gr/week for 12 weeks or placebo	The efficacy measures were physician assessment of disease activity, patient assessment of disease activity, number of swollen and tender joints, and time to resolution of arthritis	No statistical difference for clinical and laboratory parameters of disease activity and for time to recovery between the treatment groups
Combination therapy					
Carter (2004)	Double-blind, randomised	30 Chronic (>6 months) undifferentiated SpA	Doxycycline for 9 months *vs*. Doxycycline plus Rifampin for 9 months	Clinical assessment (number of tender and swollen joints, VAS for current amount of back pain, duration of MS, back pain at night, and peripheral joint pain) at baseline and at 1, 3, 6, and 9 months; Response rate (defined as improvement >20% in at least 4/6 mentioned variables compared to their baseline)	Improvement of all the variables included in the clinical assessment and higher response rate in the combination treatment group
Carter (2010)	Double-blind, randomised	42 Chronic (>6 months) *Chlamidia* ReA	3 groups: 1. Doxycycline plus Rifampin for 6 months 2. Azithromycin for 5 days followed by Azithromycin plus Rifampin for 6 months 3. Placebo	Clinical assessment (number of tender and swollen joints, VAS for current amount of back pain, duration of MS, global health, and peripheral joint pain) at baseline and at 6 months; Response rate (defined as improvement >20% in at least 4/6 mentioned variables compared to their baseline)	Significant higher response rate in the combination treatments groups compared to placebo. Significant improvement in the modified swollen joint count, tender joint count, physician global assessment in the combination treatments groups compared to placebo.
Kuuliala (2013)	Double-blind, randomised	56 Acute (<2 months) ReA (9 uroarthritis, 47 enteroarthritis)	Ofloxacin plus Roxitromicin for 3 months *vs*. placebo	Clinical and laboratory improvement at 6 months, recovery from the arthritis (no tender or swollen joints)	No advantage in treatment group in term of recovery, clinical manifestations and markers of inflammation in the treatment group

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PGA: patient global assessment; VAS: visual analogue scale; MS: morning stiffness; SpA: spondyloarthritis.

coids may be useful (9, 73). In the case of recurrent uveitis not responding to topical treatment, as well as cardiac involvement in the form of heart conduction disturbances, systemic glucocorticoid administration is recommended (74). Anti-TNF showed high efficacy and a good safety profile in the treatment of recurrent uveitis, refractory to other therapies (75).

Future perspectives

In recent years, the new insights on ReA pathogenesis, including the evidence of a persistent state of metabolically aberrant *Chlamydia* in affected joints, opened novel possible fields of research. This, together with recent data from antibiotic combination trials and biological drugs, have led to new possibilities in the potential therapeutic approach to ReA.

The use of long-term antibiotic treatment for patients with ReA is controversial. Many classes of antibiotics which are active against intracellular pathogens have been used (see Table II). the first reports on the efficacy of tetracycline for ReA date back to the early 90s, when a small study on use of minocycline in patients with *Chlamydial* ReA showed a clinical advantage in patients treated with a 3-month antibiotic course. These results were confirmed by a subsequent randomised, placebo-controlled trial on the use of a 3-month course of lymecycline, which showed beneficial effects on the duration of arthritis and on laboratory markers of inflammation in patients treated with the antibiotic compared to placebo. However, subsequent follow-up studies of the same patients for 10 years from the onset of the arthritis showed that early long-term treatment with lymecycline did not alter the natural history of the disease. The explanation of the short-term efficacy in ReA has been linked to the ability of tetracyclines, especially when used in association with NSAIDs, to inhibit the oxidative activation of latent neutrophil collagenase, to the intrinsically anti-collagenolytic effect of the drugs and to the ability to modify neutrophil functions (76).

Studies on long-term ciprofloxacin or azithromycin monotherapy showed a lack of efficacy. Few reports on the clinical advantage of ciprofloxacin use have been reported. Sieper *et al*. reported a clinical advantage in patients with *Chlamidial* ReA treated with ciprofloxacin compared with the placebo group. However, due to the small sample size of the study, none of the outcomes reached statistical significance. Another small study on 18 patients with *Yersinia*-induced ReA showed a faster recovery in patients treated with antibiotics, but the small sample size prevented drawing definitive conclusions. Interesting results have been reported by Yli-Kerttula *et al*. on the follow-up of patients who originally participated in a study evaluating the efficacy of ciprofloxacin in the early phases of ReA. During the follow-up, 41% of the patients in the original placebo group developed chronic rheumatic disease *versu*s only 8% of patients originally treated with a 3-month ciprofloxacin course, suggesting the ability of long-term antibiotic treatment administered in acute phase to prevent the chronic evolution of the disease, especially in HLA-B27 positive patients. None of the patients in the ciprofloxacin group developed manifestations of chronic SpA such as AS, inflammatory back pain, chronic oligoarthritis, enthesitis or recurrent anterior uveitis.

This apparent paradoxical capacity of ciprofloxacin to prevent chronic evolution over a long-term period despite no advantage in the short term is difficult to explain, so more long-term follow-up studies with larger samples are needed. A recent systematic review and meta-analysis of 12 clinical trials on the antibiotic treatment of ReA demonstrated no significant beneficial effect of antibiotics on remission and clinical features of the disease, in spite of a significant increase in the incidence of adverse events. However, important heterogeneity in trial design, from eligible patient selection to type and duration of treatment administered, has limited a univocal interpretation of pooled results (77). Consequently, the role of antibiotic treatment is actually uncertain, but since the majority of the trials demonstrated a lack of efficacy, long-term antibiotic monotherapy is not recommended. More recently, the demonstration of metabolically aberrant *Chlamydia* as the leading cause of *Chlamydia*-induced ReA and the resistance of this pathogen to usually effective antibiotic monotherapy, suggested the use of a combination of antibiotic drugs, which in *in vitro* showed an increased anti-chlamydial activity (78).

The first study that showed therapeutic benefit with combination antimicrobials in chronic inflammatory arthritis, possibly due to persistent *Chlamydia,* was published in 2004 by Carter *et al*. In this study, 30 undifferentiated SpA patients with no evidence of inflammatory bowel disease, psoriasis, ankylosing spondylitis, or preceding dysentery, were randomised to receive a 9-month doxycycline or doxycycline plus rifampin course. The combination therapy arm showed a statistically significant improvement compared with the single therapy arm. In a subsequent study by the same authors, chronic ReA patients with PCR-proven peripheral blood cells or synovial *Chlamydia* positivity, which is proof of persistent infections, were randomly allocated to three groups, one treated with doxycycline plus rifampin association, one treated with azithromycin plus rifampin association and the last receiving placebo. A significant greater clinical response (63% *vs*. 22%) was observed in combination treatment groups, with 20% of patients achieving complete remission compared to none of the placebo group. On the contrary, Kuuliala reported no significant benefit from combination treatment with ofloxacin and roxitromicin compared to placebo. This result could be related to antibiotic regimen choice. *Chlamydia* aberrant state seems to be resistant to conventional antibiotic therapy, therefore a combination of antibiotics, which targets different bacterial metabolic processes, is needed to obtain a significant antibacterial effect. Kuuliala *et al*. used an association between roxitromycin and ofloxacin; the latter is a fluoroquinolone drug targeting bacterial DNA replication which may be ineffective in treating the persistent form of *Chlamydia* because of its low replication activity, promoting instead a persistent viable state (79).

On the contrary, association between antibiotics that block *Chlamydia*'s protein synthesis, such as tetracycline or macrolide, with rifampin, which has the capacity to attenuate *Chlamydia*'s gene transcription, may obtain a synergistic effect on bacteria eradication (78). Satisfactory *in vitro* results have been obtained with this antibiotic combination, and the results observed in the clinical trial cited above could represent *in vivo* translation of the laboratory evidence, opening for the first time a prospective curative aetiologic treatment. However, newer and larger studies are needed to confirm this therapeutic approach.

Additional evidences about the immunological features of ReA have been obtained. ReA seems to be a Th2 mediated disease, as attested by higher levels of IL-10 and lower levels of IFNγ and TNF-α, at least at the beginning of the disease. This cytokine imbalance may contribute to bacterial persistence in affected joints. Changes in the Th1/Th2 balance may explain the relapsing course frequently seen in chronic ReA (51). In quiescent disease, the levels of Th1 cytokines are several fold lower than in active disease, suggesting that this group of cytokines may be responsible for acute inflammatory manifestations of the disease (80). This apparently dual effect of TNF-α and other Th1 cytokines raised the concern that TNF-α inhibitors might worsen intracellular bacteria growth, leading to possible dissemination of microorganisms. The identification of a newer, safer molecular target could lead to obtaining a good symptomatic control of disease, thus limiting safety issues. A recent case report described a successful treatment of a patient with ReA with tocilizumab (81). Elevated IL-6 levels in ReA patients' serum have been reported, and higher synovial fluid levels of IL-6 in patients with ReA compared to patients with rheumatoid arthritis have been described. Thus, IL-6 may be an important mediator of ReA joint inflammation. (82-84). Th17 lymphocytes appear to be, together with Th1 lymphocytes, the main inflammatory cells implicated in ReA (83). Tocilizumab may act not only by blocking IL-6 induced inflammatory response, but also by limiting inflammatory reactions related to the IL-17 pathway. In the context of SpA treatment, targeting Th17 has shown promising results. Secukinumab, an anti-IL17A antibody, was effective in AS treatment, while ustekinumab, a fully human monoclonal antibody direct against p40 subunit common to both IL-12 and IL-23, and consequently able to inhibit both Th1 and Th17 lymphocytes differentiation, yielded positive results in psoriatic arthritis (85-86). Currently, however, these agents have never been tried in ReA treatment. As for tocilizumab, adequate clinical trials for the potential application of these agents in ReA are needed.

Conclusions

Recent advances in understanding the pathogenetic events involved in ReA open the way to new exciting possibilities in the identification of potential treatments of this disease. However, many unsolved points needs to be clarified, both in the definition of the disease and in clear therapeutic strategies. Results from recent trials on antibiotic combination offer a new scenario in which a therapy targeting the inflammatory aspects of the disease could be coupled with an actual aetiologic treatment. Finally, reports of efficacy of the new biologic agents offer the possibility to enrich the therapeutic options at our disposal, mostly for patients with refractory disease.

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