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Published in:
Biomedicine & Pharmacotherapy

DOI:
10.1016/j.biopha.2022.112687

Publication date:
2022

Document version:
Final published version

Biomedicine & Pharmacotherapy 148 (2022) 112687

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Comparison of immune checkpoint inhibitor-induced arthritis and reactive arthritis to inform therapeutic strategy

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ARTICLE INFO

Keywords:
Immune checkpoint inhibitor induced inflammatory arthritis
Immunotherapy
Immune checkpoint inhibitor
Reactive arthritis
Immune related adverse events
Autoimmunity
Cancer

ABSTRACT

Introduction: Immune checkpoint inhibitor-induced inflammatory arthritis (ICI-IA) is a relatively new disease entity caused by ICI agents during cancer therapy. Reactive arthritis (ReA) is a well-known disease entity caused by urogenital or gastrointestinal bacterial infection or pneumonia. In this sense, ICI-IA and ReA are both defined by a reaction to a well-specified causal event. As a result, comparing these diseases may help to determine therapeutic strategies.

Methods: We compared ICI-IA and ReA with special focus on pharmacological management. Specifically regarding treatment, we conducted a literature search of studies published in the PubMed database. Inclusion criteria were studies on treatment with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), or disease modifying antirheumatic drugs (DMARDs) in ICI-IA or ReA. During systematic selection, 21 studies evaluating ICI-IA and 14 studies evaluating ReA were included.

Results: In ICI-IA, prospective and retrospective studies have shown effects of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoid (GC), sulfasalazine (SSZ), methotrexate (MTX), hydroxychloroquine (HCQ) and TNFi. In ReA, retrospective studies evaluated NSAIDs and GC. A randomized controlled trial reported the effect of SSZ, and a retrospective study reported the effect of MTX and SSZ in combination with tumor necrosis factor alpha inhibition (TNFi). For both entities, small case reports show treatment effects of interleukin 6 receptor inhibition (IL-6Ri).

Discussion: This literature review identified both similarities and differences regarding the pathogenesis and clinical features of ReA and ICI-IA. Studies on treatment reported effectiveness of NSAIDs, GC, MTX, SSZ and TNFi in both diseases. Further, small case reports showed effects of IL-6Ri.

Abbreviations: ACPAs, Anti-citrullinated protein antibodies; AZA, Azathioprine; bDMARDs, Biologic disease-modifying antirheumatic drugs; csDMARDs, Conventional synthetic disease-modifying antirheumatic drugs; CTLA4, Cytotoxic T-lymphocyte-associated protein 4; DMARD, Disease-modifying antirheumatic drugs; GC, Glucocorticoid; GC ia, Glucocorticoid intra articular; GC sys, Glucocorticoid systemic; HCQ, Hydroxychloroquine; IA, Inflammatory arthritis; ICIs, Immune checkpoint inhibitor(s); ICI-IA, Immune checkpoint inhibitor-induced inflammatory arthritis; IL-6Ri, interleukin 6 receptor inhibition; IL17, Interleukin 17; irAEs, Immune related adverse event(s); JAK, Janus kinase; JAK-i, Janus kinase inhibitor; MTX, Methotrexate; NSAIDs, Non-steroidal anti-inflammatory drug(s); PD1, Programmed cell death protein 1; PDL1, Programmed death-ligand 1; RCT, Randomized controlled trial; ReA, Reactive arthritis; RF, Rheumatoid factor; rirAEs, Rheumatic immune related adverse event(s); SSZ, Sulfasalazine; TCZ, Tocilizumab; TNFi, TNF inhibitor.

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https://doi.org/10.1016/j.biopha.2022.112687
Received 18 November 2021; Received in revised form 31 January 2022; Accepted 1 February 2022
Available online 25 February 2022

1. Introduction

Immune checkpoint inhibitor-induced inflammatory arthritis (ICI-IA) is an immune-related adverse event (irAE) caused by ICI treatment. Reactive arthritis (ReA) is a well-known disease entity usually triggered by a urogenital or gastrointestinal bacterial infection or seldomly by pneumonia. ICI-IA and ReA are in this way both characterized by a synovial reaction to a well-defined causal event. Since ICI-IA is a new disease entity, it is interesting to evaluate if treatment strategies for ICI-IA could be inspired by treatment of ReA. Here, we compare ICI-IA and ReA triggers, underlying immunology, and clinical features and conduct a literature search of studies on pharmacological management.

ICIs are monoclonal antibodies targeting either the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) or the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway. CTLA-4 and PD-1 are co-inhibitory molecules that negatively regulate T cell activity and are therefore often termed immune checkpoints. Blocking these pathways leads to increased activity of the immune system, which promotes the development of irAEs. [1,2] The pathogenesis of irAE is not fully understood. irAE and their severity are driven by a variety of immunological mechanisms including cells from the adaptive and innate immune system mediating organ damage, either directly through self-recognition or indirectly through uncontrolled inflammation in normal tissue. The effector mechanism in anti-cancer therapy with immune checkpoint inhibitors is overall a CD8+ Tc cell activation. [3] In contrast, immune mediated inflammatory diseases (autoimmune diseases) are characterized by activation of many different parts of the immune system. Some immune-mediated inflammatory diseases are clearly driven by macrophages while other immune-mediated inflammatory diseases are driven by B cells and autoantibody production. Not much is known about the immune activation in immune related adverse events. Environmental factors also shape the immune response to ICI and the development of irAEs. [4] In this regard, the commensal microbiota is also suspected to influence both the efficacy and toxicity of ICI. [5–7].

ReA is an inflammatory disease of the joints secondary to urogenital, gastrointestinal or pulmonary bacterial infection. [8,9] The most common infectious agents are *Chlamydia trachomatis*, *Salmonella*, *Shigella*, *Campylobacter jejuni* and *Yersinia*. [9,10] Although the association between HLA-B27 and infectious agents has been known for decades, the pathogenesis of ReA is, like that of ICI-IA, not fully understood. Evidence from human and animal studies suggest a role for post-infectious dysregulation of the gut microbiome and host-microbe interaction in the pathophysiology of ReA, in which also defects in the gut mucosal barrier have been implicated. [11] The pathogenesis is still not fully understood. Th17 cells producing IL-17 have been suggested as one of the effector cells. However, many other cells and cytokines have been implicated including TNFα, IL-23 and IL-6. [12].

The incidence of ICI-IA is between 1% and 7% (Table 1). [2,13–15] However, arthralgia is reported in up to 40% of patients treated with ICIs. [2,16,17] There is obviously a possibility of sublinical synovitis in some of these patients. The median time from ICI initiation to development of ICI-IA symptoms is 5–6.5 months. [18,19] ICI-IA is often polyarticular (64%), but can be oligoarticular (24%) or monoarticular (13%). [20] ICI-IA typically affects joints in the upper extremities with involvement of the shoulder (50%), the cubital joint (13%), the wrist (40%), the metacarpophalangeal joints (49%) or the proximal interphalangeal joints (50%). In the lower extremities, the most often affected joints are the knees (42%), followed by the ankle joints (18%) and the metatarsophalangeal joints (8%). Involvement of the sacroiliac joint are also seen (22%). [21] Some studies report that up to 79% of patients present with involvement in both large and small joints. [22] Furthermore, some patients have dactylitis (3%−8%) and enthesitis (5%). [18,23–27] Studies have shown seropositivity for rheumatoid factor in 5% and for anti-citrullinated protein antibodies in 5.5% of patients with ICI-IA. In a few studies, these seropositive ICI-IA patients were compared to the clinical diagnosis criteria for rheumatoid arthritis (RA) and only a few patients met classification criteria. [1,18,23,28] There is also limited evidence on the genetics of ICI-IA. One study reported increased risk of developing ICI-IA in patients with at least one RA-associated shared epitope (SE) allele. The risk allele with the strongest association was HLA DRB1 * 04:05. [29] Several studies have shown that HLA-B27 is not associated with the development of ICI-IA. [1,29] Many patients with ICI-IA also have additional irAEs (Table 2). One study found that patients who developed ICI-IA after combination immunotherapy of nivolumab and ipilimumab all had colitis. [18] Other studies found a varying degree of colitis in ICI-IA patients (6%−44%). Several other irAEs have been observed concomitantly in ICI-IA patients, including rash and dermatitis (14%−50%), thyroiditis (6%−33%), pneumonitis (6%−18%), hypophysitis (6%−10%), and psoriasis (9%). [14,18,23,27,28,30–32] One study described persistence of ICI-IA in 49% of ICI-IA patients up to 6 months after ICI treatment had been stopped. [27] However, studies with longer follow-up are lacking. Therefore, long-term prognosis for ICI-IA is difficult to assess.

The incidence of ReA has been estimated to be between 1% and 1.5% after gastrointestinal infection [10,33] and between 3% and 8% after urogenital tract infections (2 studies with follow-up after Chlamydia trachomatis infection and one study after Neisseria gonorrhoea infection) (Table 1) [34]. Time from infection to symptom onset is usually one to four weeks. [35–37] ReA is most commonly oligoarticular (72%),

Table 1
Clinical characteristics of ReA and ICI-IA:.

	ReA	ICI-IA
Incidence	1%− 1.5% after GI infection [10,33] and 3%− 8% after UG infection.[34]	1%− 7% of cancer patients treated with ICI. [2,13–15]
Time of onset	From days to several weeks. [35–37]	5–6.5 months after ICI initiation. [18,19]
Joints distribution	Monoarticular type (13%), oligoarticular type (72%) or polyarticular type (15%). [38]	Monoarticular type (13%), oligoarticular type (24%) or polyarticular type (64%). [20]
	Upper extremities: Shoulder (5%), cubital joint (5%), wrist (23%), metacarpophalangeal joints (17%) or proximal interphalangeal joint (8%). [38]	Upper extremities: Shoulder (50%), cubital joint (13%), wrist (40%), metacarpophalangeal joints (49%) or proximal interphalangeal joint (50%). [21]
	Lower extremities: Knee (63%), ankle (55%) or metatarsophalangeal joints (47%). [38]	Lower extremities: Knee (42%), ankle (18%) or metatarsophalangeal joints (8%). [21]
	Involvement of the lumbar spine (up to 50%) and sacroiliac joints (15%−30%). [39]	Involvement of the sacroiliac joint (22%). [21]
Dactylitis	16%. [9,10,37,39,40]	3%− 8%. [18,23–27]
Enthesitis	22–30%. [9,10,37,39,40]	5%. [18,23–27]
Genetics	Strong HLA-B27 association. [10]	No HLA-B27 association. [1,29]
		At least one RA-associated SE allele (HLA DRB1 *04:05 with strongest association). [29]
Prognosis	> 90% self-limiting (average symptom duration 3–5 months). [36]	Varying and not fully elucidated. In one study, 49% ICI-IA patients still had ICI-IA after 6 months follow-up. [27]

UG infection; 2 studies with follow-up after Chlamydia trachomatis infection and one study after Neisseria gonorrhoea infection.

but can be monoarticular (13%) or polyarticular (15%). [38] ReA typically affects joints in the lower extremities with involvement of the knees (63%), the ankle joints (55%) or the metatarsophalangeal joints (47%). Involvement of joints in the upper extremities are also seen with involvement of the shoulders (5%), the cubital joints (5%), the wrists (23%), the metacarpophalangeal joints (17%) or the proximal interphalangeal joints (8%). [38] Involvement of the lumbar spine (up to 50%) or sacroiliac joints (15%−30%) is also seen. [39] Furthermore, ReA can present with dactylitis (16%) or enthesitis (22–30%). [9,10,37,39,40] No definitive antibodies have been associated with ReA. [1] HLA-B27 positivity is found in 50%− 80% of ReA patients, [10] and HLA-B27-positive patients have a higher incidence of ReA. [41] Extra-articular manifestations are typically conjunctivitis (35%), iritis (5%) and rash (up to 60%) (Table 2). [42] ReA is self-limiting in more than 90% of patients with an average duration of acute ReA symptoms of 3–5 months. [36].

Taken together, the immunological mechanisms underlying ICI-IA and ReA seems to be very different which is also reflected by very divergent extra-articular manifestations. However, ICI-IA and ReA are both characterized by a well-defined inflammatory trigger that induces arthritis with latency of several weeks and can be self-limiting. Further, the two disease entities also share some clinical features including involvement of large joints, and entheses. Therefore, a comparison of the treatment of these diseases could inform therapeutic strategies in ICI-IA. [2,8,9,13].

2. Methods

2.1. Search strategy

A search of existing literature was done using the PubMed database including publications up to August 2021. The search strategy included a combination of '*terms of disease*' and '*terms of treatment*'. This was done for both ICI-IA and ReA (supplementary materials S1 and S2). PubMed filters were used to identify studies of interest. Included in this review were 'randomized controlled trial (RCT)', 'observational study', 'multicenter study', 'controlled clinical trial', 'clinical trial', 'clinical trial phase I/II/III/IV', 'clinical study' and 'case reports'. Only studies in English language were included. Additionally, a manual search using reference lists from relevant literature was performed.

2.2. Study selection

Study selection was done by reading titles and abstracts. Inclusion criteria were studies on treatment with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), or disease modifying antirheumatic drugs (DMARDs) in ICI-IA or ReA (addendum S1 and S2). Included were studies with the largest cohort evaluating each specific treatment. Flowcharts of the selection process for ICI-IA and ReA studies are presented as supplementary materials S3 and S4.

3. Results

For ICI-IA treatment, a total of 669 studies were found using the PubMed database and 37 studies were found during the manual search. For ReA treatment, a total of 872 studies were found using the PubMed database and an additional 21 studies were identified during the manual search. After the study selection procedure, 21 studies on treatment of ICI-IA and 14 studies on treatment of ReA met the inclusion criteria (Tables 3 and 4).

3.1. ICI-IA studies

Braaten et al. (2019) [27] (Table 3) reported a prospective observational cohort study including 60 ICI-IA patients. This is the largest cohort of ICI-IA patients to date, and the first study to evaluate persistence of ICI-IA through follow-up. Treatment of ICI-IA consisted of GC monotherapy in 16 patients (27%) and NSAIDs monotherapy in seven patients (12%). Concomitant csDMARDs were used in 19 patients (32%), including sulfasalazine (SSZ), methotrexate (MTX), azathioprine

Table 2
Extra articular manifestations in patients with ICI-IA or ReA [14,18,27,30–32,40,42].

	ICI-IA						ReA
	Braaten (2020)[27]	*Capelli (2018)*[18]	*Liu (2020)*[31]	*Mitchell (2018)*[32]	*Le Burel (2017)*[30]	*Lidar (2018)*[14]	*García-Kutzbach(2018), Stav-ropoulos (2015)*[40,42]
Included patients.:	60	30	20	18	12	11	
Colitis:	17%	33%	20%	6%	8%	18%	
Dermatitis/rash:	17%	13%	50%	22%			60%
Thyroiditis:	13%	17%		6%	16%	9%	
Pneumonitis:	10%	13%	10%	6%	8%	18%	
Hypophysitis:	7%	7%	10%	6%			
Psoriasis:						9%	
Gastritis:						9%	
Pancreatitis:	2%	3%		6%			
Hepatitis:	7%				16%	18%	
Sicca:	12%	10%					
Conjunctivitis:							35%
Iritis:							5%
Myocarditis:		3%					
Myositis:							

For the selection of studies reporting extra articular manifestations in ICI-IA, we included only studies with more than 10 patients.
Grey fields = manifestation not reported.

Table 3
Included studies on treatment of ICI-IA [2,13,14,18,19,22,23,27,28,30,31,43,44,46–48,50,57,58,69,70].

ICI -IA studies:

Study information :				Treatment:									
Author:	**Year:**	**Design:**	**Patients**	**NSAID:**	**GC-sys:**	**GC-ia:**	**SSZ**	**MTX**	**HCQ**	**AZA**	**TNF-i**	**IL6-Ri**	**JAK-i**
Braaten[27]	2020	P	60	7 *	16 *		19 Δ				11 Δ		
Richter[57]	2019	R	34	8 ‡			1 Δ	2 ‡	1 Δ	1 Δ		1 Δ	
Capelli[18]	2018	R	30		24 ‡			3 Δ			7 Δ		
Kostine[2]	2018	P	20	2 *	16*			2 Δ					
Liu[31]	2020	R	20		15 *			1 *	2 *				
Leipe[46]	2018	P	14	2 *	9 ‡	8 ‡	1 Δ	6 Δ					
Capelli[22]	2020	S	14	4 ‡	12 ‡		2 Δ	5 ‡			4 Δ		
Le Burel[30]	2017	R	12		9 *			2 *					
Mooradian[58]	2019	R	12		10 ‡	4 Δ	5 Δ		7 ‡				
Liew[43]	2019	R	11		8 *		3 *						
Roberts[19]	2019	R	11		5 Δ	6 Δ			11 ‡				
Lidar[14]	2018	R	11	10	11 ‡			7 Δ					
Belkhir[69]	2017	R	10	3 ‡	7 ‡			1 Δ	2 Δ				
Buder-Bakhaya[13]	2018	R	10	6 *	4 Δ		2 ‡						
Smith[44]	2019	R	10		10 ‡		3 Δ				1 Δ		
Capelli[23]	2017	R	9	1 Δ	6 ‡	5 Δ		1 Δ			4 ‡		
Calabrese[28]	2017	R	7		7 ‡			2 Δ	1 Δ		2 Δ		
Verspohl[47]	2021	R	7		7 ‡			3 Δ				1 Δ	
Narváez[70]	2018	P	5	5 ‡	4 Δ				3 Δ				
Kim[48]	2017	C	3									3 *	
Murray[50]	2021	C	1					1 Δ					1 Δ

Numbers indicating how many patients receiving and responding concerned treatment.
Study design: P = Prospective study. R = Retrospective study. C = Case report. S = Semi-structured interview.
Drugs: NSAID = non-steroidal anti-inflammatory drugs. GC sys = glucocorticoid systemic. GC ia = glucocorticoid intra articular. csDMARD = conventional synthetic disease-modifying antirheumatic drugs. SSZ = Sulfasalazine. MTX = Methotrexate. HCQ = Hydroxychloroquine. AZA = Azathioprine. bDMARD = biologic disease-modifying antirheumatic drugs. TNFi = TNF alpha inhibitor. IL-6Ri = IL-6 inhibitor. JAK-i = JAK inhibitor.

Colour / symbol	Description:
Dark green:	Efficacy in RCT
Light green:	Efficacy in prospective study
Yellow:	Efficacy in retrospective study
Orange:	Efficacy in case report
Red:	No efficacy demonstrated.
Light grey:	Not reported.
*	Efficacy in monotherapy.
Δ	Efficacy in combination.
‡	Efficacy alone or in combination.

(AZA) and hydroxychloroquine (HCQ). Concomitant therapy with TNFi was used in 11 patients (18%). Patients were followed for up to 24 months, with a median of nine months. Several of the treatments were effective but differences between the DMARDs were not assessed. *Capelli* et al. *(2018)* [18] (Table 3) presented a retrospective study including 30 ICI-IA patients. GC therapy was used in a total of 24 patients (80%), including fourteen patients (47%) in GC monotherapy, with clinical improvement. The remaining 10 patients (33%) received concomitant treatment with GC (three patients (30%) received MTX and seven patients (23%) received TNFi with or without MTX); all had clinical improvement of ICI-IA and none of the patients had tumor progression. The same clinical effect of GC monotherapy was shown in several other studies. [2,30,31,43–45] *Leipe* et al. *(2018)* [46] (Table 3) reported a prospective cohort study including 14 ICI-IA patients. Two patients (14%) were treated with NSAID monotherapy. Two patients (14%) were treated with GC monotherapy. Three patients (21%) had intra articular GC monotherapy. Five patients (36%) were treated with combination GC and MTX, and one patient (7%) was treated with combination GC, MTX, and SSZ. The study found profound effect of all treatments and reported that MTX was an effective GC-sparing agent in ICI-IA. The clinical effect of MTX as combination therapy has also been shown in several other studies. [2,14,18,28] *Verspohl* et al. described 163 patients with irAEs including seven patients with ICI-IA of whom all patients (100%) were treated with GC. In four cases additional therapy with MTX

Table 4
Included studies on treatment of ReA [51–56,71–78].

ReA studies:													
Study information :				Treatment:									
Author:	Year:	Design:	Patients	NSAID:	GCsys:	GCia:	SSZ	MTX	HCQ	AZA	TNFi	IL6-Ri	JAK-i
Clegg[51]	1996	RCT	134	69			69 *						
Thorsteinsson[52]	2020	R	38	34							38 *		
Flagg[55]	2005	R	16	16	7		8	7	5		16 *		
Brinster[54]	2017	R	15	15	11		6	10			15 *		
Meyer[53]	2011	R	10	7 Δ	8 Δ		2 Δ	8 Δ			10 Δ		
Oili[71]	2003	C	2		2		2	2			2 *		
Tanaka[56]	2009	C	1									1 *	
Courcoul[72]	2017	C	1	1			1				1 *		
Sanchez-Cano[73]	2007	C	1								1 *		
Grill[74]	2008	C	1								1 *		
Wechalekar[75]	2010	C	1								1 *		
Schafranski[76]	2010	C	1								1 *		
Edrees[77]	2012	C	1								1 *		
Thomas-Pol[78]	2012	C	1								1 *		

Numbers indicating how many patients receiving and responding concerned treatment.
Study design: RCT = Randomized, controlled trial. P = Prospective study. C = Case report.
Drugs: NSAID = non-steroidal anti-inflammatory drugs. GC sys = glucocorticoid systemic. GC ia = glucocorticoid intra articular. csDMARD = conventional synthetic disease-modifying antirheumatic drugs. SSZ = Sulfasalazine. MTX = Methotrexate. HCQ = Hydroxychloroquine. AZA = Azathioprine. bDMARD = biologic disease-modifying antirheumatic drugs. TNFi = TNF alpha inhibitor. IL-6Ri= IL-6 inhibitor. JAK-i = JAK inhibitor.

Colour / symbol	Description:
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Orange:	Efficacy in case report
Red:	No efficacy demonstrated.
Light grey:	Not reported.
*	Efficacy in monotherapy.
Δ	Efficacy in combination.
‡	Efficacy alone or in combination.

or the interleukin-6 receptor inhibitor (IL-6Ri) tocilizumab (TCZ) was required. [47] *Roberts* et al. *(2019)* [19] (Table 3) was a retrospective study including 11 ICI-IA patients treated with HCQ. They were all treated with HCQ, either in monotherapy (n = 3 (27%)) or with concomitant intra-articular GC (n = 3 (27%)), systemic GC (n = 3 (27%)) or combination of intra articular and systemic GC (n = 3 (27%)). Seven of 11 patients (64%) had a full response to therapy, 3 patients (27%) had a partial response, and one patient (9%) was lost to follow-up. The authors concluded that HCQ appears to be a safe and effective steroid-sparing treatment for ICI-IA. *Kim* et al. *(2017)* [48] (Table 3) was a case report including three patients with ICI-IA treated with the TCZ. Two cases were treated with systemic GC initially with insufficient effect. All three patients had significant clinical improvement of symptoms on TCZ. Interestingly, increased risk of drug hypersensitivity reaction to SSZ has been reported in a case series of four patients with ICI-IA. [49] A recent case report has shown effect of Janus kinase (JAK) inhibition in ICI-IA. [50].

3.2. ReA studies

Clegg et al. *(1996)* [51] (Table 4) evaluated the use of SSZ in a randomized, double-blind, placebo-controlled study including a total of 134 patients. Sixty-nine patients (51%) were treated with SSZ and 65 patients (49%) were treated with placebo. This study found a response to treatment in 62% of cases treated with SSZ and in 48% of cases treated with placebo, leading to the conclusion that SSZ is a well-tolerated and effective treatment of ReA. *Thorsteinsson* et al. *(2020)* [52] (Table 4) was an observational cohort study supplemented with a retrospective study including 38 ReA patients treated with TNFi. This is the largest study on treatment options for ReA apart from studies examining antibiotic treatment. Thirty-four of 38 patients (89%) had tried NSAIDs and previously failed conventional synthetic DMARDs. TNFi therapy was safe and effective in ReA with significant improvement of arthritis and reduction of C-reactive protein levels at both 6- and 18-month follow-up visits. The results of this study are supported by several studies with fewer participants. [53–55] In all these studies, patients had failed on NSAIDs and conventional synthetic DMARDs (MTX, SSZ, or HCQ). TNFi was effective and well-tolerated as treatment for ReA. Further, several case reports have shown clinical improvement of symptoms during TNFi treatment in monotherapy. *Tanaka* et al. *(2009)* [56] (Table 4) is a case report including one patient treated with the IL-6Ri TCZ following failure with GC and DMARDs. Symptoms improved following IL-6Ri treatment.

4. Discussion

ICI-IA and ReA show many differences including immunological mechanisms and extra-articular manifestations. However, because of shared disease course with an inflammatory trigger and a potential for a self-limiting synovitis we investigated the current studies on treatment of the two disease entities. This literature search identified 21 studies on the treatment of ICI-IA and 14 studies on the treatment of ReA.

In ReA treatment, only one retrospective study reported positive effects for NSAIDs and GC [53], while all other ReA studies included patients with previous failure on NSAIDs and GC. Effect of NSAIDs and GC was reported in ICI-IA in several studies. [2,14,18,27,48,57] For example, an effect of NSAID monotherapy was seen in between 10% [2] and 12% [27] of patients with ICI-IA. However, it is not possible to draw any conclusions regarding the effect of NSAIDs and GC in either ICI-IA or ReA. Likely, patients with a self-limiting disease course can be managed by these medications while DMARDs will be required in persistent disease. In addition, the risk of publication bias should be considered.

Concerning treatment with DMARDs, there are similarities in effect between ReA and ICI-IA in the included studies. The studies in this review included treatment with MTX, SSZ, HCQ, TNFi and IL-6Ri. *Clegg* et al. *(1996)* [51] reported better effect of SSZ than placebo in ReA and another study [53] showed a positive effect of MTX and SSZ in combination with TNFi in ReA. Several prospective and retrospective studies reported effects for MTX, [14,18,22,27,46,57] HCQ [19,27,31,57,58] and SSZ [22,46,57,58] in ICI-IA. The effectiveness of DMARDs in both conditions implies that similarities in treatment effect of conventional synthetic DMARDs in ReA and ICI-IA are likely. [8,14,59] However, while there is evidence to support the use of SSZ in ReA this treatment has been associated with hypersensitivity reactions in ICI-IA. [49] Regarding bDMARDs, TNFi has been shown to be beneficial in both ReA [52–56] and ICI-IA [18,22,23,27,48], which suggests that TNF plays a pathophysiological role in both entities. Of note, treatment with TNFi has been more rigorously studied in ReA than treatment with conventional synthetic DMARDs.

There are other interesting candidates for the treatment of ICI-IA, including IL-6Ri, which could be a promising treatment option. However, IL-6Ri was only examined in a few case reports for both ICI-IA and ReA. Another interesting perspective for future treatment of ICI-IA is the use of anti-CD20 antibodies. We have previously reported that development of ICI-induced thyroiditis was decreased in patients managed with a haematologic treatment protocol of ICI treatment together with B cell depletion compared with the historical data of ICI monotherapy. [60] This is in line with a previous study showing that early changes in B cells following ICI could identify patients at increased risk of irAEs. [61] However, it is important to consider that ICI-IA is not typically associated with the production of autoantibodies. Therefore, B cell depletion might not be a rational therapeutic option. Therapies targeting the IL-23-Th17 axis might be another option. This is a particularly interesting therapeutic avenue because ICI-IA cases often resemble the joint involvement seen in spondyloarthritis.

There is a concern that the use of immunosuppressants may reduce the anti-cancer efficacy of ICI treatment. A retrospective study on patients with ICI-induced hypophysitis showed that patients treated with high dose GC to prevent destruction of the pituitary gland had a lower overall survival than those merely receiving substitution dosage [62]. Further, baseline GC dose $\geq$ 10 mg prednisone equivalent at ICI initiation were associated with lower survival rates [63]. The safety of bDMARDs for traditional rheumatic diseases in patients with previous or current cancer disease have been debated [64,65]. Thus, the indication and choice of immunosuppressants in cancer patients treated with ICI is challenging and require collaboration with oncologists.

A European guideline for sexually-transmitted ReA was published in 2014 [66] but has not been updated since. [9] For now, recommendations about ReA treatment recommend that initial treatment should consist of symptomatic treatment (NSAIDs) or GC for about three months. The next step after failure of symptomatic treatment is treatment with conventional synthetic DMARDs or a biologic DMARD. [9] According to new oncologic guidelines on the treatment of irAEs including ICI-IA, initial treatment of ICI-IA is GC (either systemic or intra articular). Treatment for patients that need long-term treatment or does not respond to GC may include TNFi, MTX, leflunomide, HCQ, or IL-6Ri. [67,68].

According to clinicaltrials.gov, several studies on the treatment of irAEs are in the recruitment phase. One study is recruiting only patients with immune-related arthritis or arthralgias for a double-blinded randomized study to evaluate the safety and efficacy of HCQ compared with placebo (clinicaltrial.gov #NCT04354649).

There are several limitations with this study. First, it would have been more logical to only include patients with a "ReA-like" phenotype of ICI-IA. However, this was not possible because of the already low number of ICI-IA studies identified. Patients with ICI-IA can also present with a phenotype more resembling rheumatoid arthritis or psoriatic arthritis. Further, it was not possible to make subgroup analysis of different treatments in the different clinical phenotypes. Second, the aim of the literature review was to identify studies on treatment of ICI-IA and ReA. Therefore, the clinical characteristics and extra articular manifestations of the two diseases are not based on a comprehensive literature search.

5. Conclusion

Taken together, this literature review revealed both differences and similarities regarding pathogenesis, clinical features, and treatment of ReA and ICI-IA. Studies reported effectiveness of NSAIDs, GC, MTX, SSZ and TNFi in both diseases. Further, small case reports showed effects of IL-6Ri. In this way we reveal the efficacy of several csDMARDs and bDMARDs in both ReA and ICI-IA. Because of the small number of studies on treatment of patients with ReA, we were not able to use these data to guide treatment protocols for ICI-IA. However, the two disease entities are relevant to manage with concordant principles due to the similarities in disease course with an inflammatory trigger and a potential for a self-limiting synovitis.

Funding

TWK was supported by a grant from Independent Research Fund Denmark (9039–00015B).

Authors' contributions

AKJ and TWK designed the project. **AKJ** performed the literature search, extracted data and evaluated quality of included studies. **AKJ and TWK** made the first draft of the manuscript. All authors helped assess methodological quality of included studies and interpret study results. All authors critically reviewed the manuscript and approved the final version.

Ethics approval and consent to participate

Not applicable.

Conflict of interest statement

T. Kragstrup has received the Gilead Nordic Fellowship grant, has engaged in educational activities receiving speaking fees from Pfizer, Bristol-Myers Squibb, Eli Lilly, Novartis, UCB, and Abbvie, has received consultancy fees from Bristol-Myers Squibb, Gilead, Galapagos, and UCB, and is co-founder and clinical developer in iBiotech ApS developing diagnostic and therapeutic solutions for people with autoimmune diseases and cancer. J. Leipe received grant/research support from: Novartis, Pfizer; Abbvie, BMS,

Gilead, Janssen, Sanofi; honoraria for consulting or speaking: Abbvie, BMS, Galapagos, Janssen-Cilag, Gilead, Lilly, Medac, MSD, Novartis, Pfizer, Roche/Chugai, Sanofi, UCB. V.Schäfer received grant/research support from: Novartis, Hexal, Lilly, Roche, Celgene, University of Bonn, honoraria for consulting or speaking: Chugai, AbbVie, Celgene, Sanofi, Lilly, Pfizer, Amgen, BMS, Roche, Gilead, Novartis, BMS, Medac, Sanofi, Lilly, Pfizer, Janssen, Roche, Schire, Onkowissen.

Data availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2022.112687.

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