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Efficacy and safety of abatacept in interstitial lung disease of rheumatoid arthritis: A systematic literature review

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ABSTRACT

Background: Interstitial lung disease (ILD) is a serious complication that represents the second leading cause of death in patients with rheumatoid arthritis (RA). Treatment of RA-ILD remains controversial. The absence of randomized clinical trials and specific ACR or EULAR therapeutic guidelines makes it difficult to establish solid therapeutic recommendations on this issue. In this scenario, real-world data is especially valuable.

Objective: To review the literature evidence on the efficacy and safety of abatacept (ABA) for the treatment of rheumatoid arthritis (RA) with associated interstitial lung disease (ILD), given its clinical relevance and the lack of consensus on its therapeutic management.

Methods: PUBMED and EMBASE were searched from the date of approval of ABA to the end of 2020 using a combination of RA, ILD and ABA terms following PRISMA guidelines. Identified studies were evaluated by two independent investigators.

Results: Nine original studies (1 case series and 8 observational studies) were selected for inclusion in the systematic review. No randomized trial or meta-analysis were identified. The mean age of patients ranged from 61.2 to 75 years and the mean RA duration varied from 7.4 to 18 years. Subcutaneous ABA (74.5%–91%) predominated in combination with conventional synthetic DMARDs (csDMARDs) (58%–75%), and it was used as first-line biologic agent in 22.8%–64.9% of the patients. The mean course of ILD ranged from 1 to 6.7 years, being usual and nonspecific interstitial pneumonia the most frequent patterns. Improvement or stabilization of ILD imaging (76.6%–92.7%) and FVC or DLCO (>85%) was described after a mean follow-up of 17.4–47.8 months, regardless of the pattern of lung involvement, being more remarkable in patients with shorter evolution of ILD. ABA led to significantly lower ILD worsening rates than TNF inhibitors (TNFi) and was associated with a 90% reduction in the relative risk of deterioration of ILD at 24 months of follow-up compared to TNFi and csDMARDs. Combination with methotrexate may have a corticoid-sparing effect. No unexpected adverse events were identified.

Conclusions: Current evidence suggests that ABA may be a plausible alternative to treat RA patients with ILD. It would be highly desirable to develop prospective randomized controlled studies to confirm these findings.

1. Introduction

Interstitial lung disease (ILD) is one of the main extra-articular manifestations of rheumatoid arthritis (RA) [1]. It is associated with a significant decrease in the quality of life of patients, worsening their prognosis and shortening survival. Clinically significant ILD occurs in

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5–10% of RA patients throughout their life course [1,2]. Its prevalence ranges from 1% to 58% depending on the diagnostic method used and the severity of the RA population studied [3] and the incidence ranges from 2.7 to 3.8 per 100,000 patients, depending on the screening method used [4]. Nowadays, ILD represents the second cause of death in RA after cardiovascular disease [5].

The course of the ILD is variable. It can remain in a stable, pauci-symptomatic state for longtime or present a rapidly progressive, even fulminant, course. The 10-year survival ranges from 20% to 40% of patients, with a median survival of 3 to 8 years [2,4]. This makes it necessary to detect the involvement in its earliest stages, since early treatment seems to be associated with a better prognosis.

At present, there is no agreement in the screening protocol for RA-ILD, although the main risk factors associated with its appearance are well-known. In particular, clinicians should be careful in the assessment of male and smoking patients, of old age, rheumatoid factor (RF) and anti-citrullinated cyclic peptide (aCCP) antibodies positivity, especially at high titer, and an hyperinflammatory condition [6].

The most sensitive and specific diagnostic tool for ILD is high resolution computed tomography (HRCT) of the chest, which allows us to identify ILD even at an early stage and distinguish between different subtypes of radiological involvement that are associated with a different prognosis. Usual interstitial pneumonia (UIP) is the most frequent pattern in RA, in contrast to connective tissue diseases (CTD) in which the non-specific interstitial pneumonia (NSIP) pattern predominates [7,8], and the one with the worst prognosis [9]. However, other authors have not found significant differences in the survival according to the underlying ILD radiological patterns [10].

Regarding the treatment of RA-ILD, the optimal strategy has not yet been established. The ability of immunomodulatory therapies to control the inflammatory activity of the disease makes plausible the hypothesis that these drugs have a potential beneficial effect on RA-ILD. However, these treatments can increase the risk of infections, which have been linked as a trigger that could increase the risk of developing or exacerbating ILD. In addition, most of the disease modifying anti-rheumatic drugs (DMARDs) used to treat RA have also been associated with a potential risk of inducing or aggravating ILD. This complication has been reported with conventional synthetic (csDMARDs) and biologic (bDMARDs) DMARDs, especially methotrexate (MTX) and TNF inhibitors (TNFi), as well as targeted synthetic therapies (tsDMARDs) [11–15]. However, some studies have shown a potential favorable role for several DMARDs in RA-ILD patients [16–19].

Abatacept (ABA) is a soluble fusion protein, comprising cytotoxic T-lymphocyte-associated protein 4 and an Fc portion of immunoglobulin G1, which inhibits T-lymphocyte co-stimulation and is approved for the treatment of moderate to severe RA. In clinical trials, ABA has demonstrated efficacy and safety in different contexts such as failure to TNFi or patients naïve to bDMARDs and csDMARDs [20,21]. Regarding the risk of inducing ILD, the data from post-marketing studies and pooled analysis of safety data from 8 clinical trials of intravenous ABA are encouraging as they show very low incidence rates of ILD, even lower than those described for RA itself and for the rest of DMARDs [22,23]. Additionally, ABA has shown a lower risk of infections requiring hospitalization in comparison with other bDMARDs [24]. In addition, in recent years, evidence has been accumulating from real-world studies on its potential utility in treating patients with RA-ILD [25–33].

Given the clinical relevance of RA-ILD, the lack of consensus on its management and the gaps in knowledge that still exist about which is the best therapeutic alternative for these patients, we have carried out this systematic review with the aim of studying the published scientific evidence to date on the efficacy and safety of ABA treatment of RA with associated ILD, based on previous considerations.

2. Methods

2.1. Data sources, search strategy and study selection

The reporting methodology of this review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [34]. Published evidence about the role of ABA in RA-ILD in PUBMED and EMBASE databases was searched by two independent investigators (E.V.R. and B.A.M.) using the following combination of terms: “rheumatoid arthritis” AND “interstitial lung disease” AND “abatacept”. The period of time between the Food and Drug Administration (FDA) approval of ABA (12/23/2005) and December 2020 (12/31/2020) was selected, adding English language and Title/Abstract fields as further limits. Abstracts were screened to select relevant articles to be fully analyzed. Given the limited number of articles concerning this topic, the inclusion criteria were as follows: a) articles describing any data about efficacy and/or safety of ABA therapy used in patients with RA-ILD; b) original studies, including case series, cross-sectional studies, cohort studies and clinical trials, either non-randomized or randomized controlled trials. We excluded congress communications and publications of isolated case reports, as well as reviews, although they were evaluated in order to detect relevant bibliographic references.

2.2. Data collection

We designed a template form to extract the considered relevant data from each selected paper that included the following items: author, year of publication, study design, period of inclusion of patients, sample size, demographic and clinical characteristics (mean age, sex, mean RA and ILD evolutions, RA-ILD classification and/or diagnostic criteria used, follow-up, previous treatments, outcome measures for RA and ILD, scores used for RA and ILD, response to treatment). The risk of bias was assessed only for observational studies, excluding case series.

3. Results

3.1. Flow chart and selected studies

The flow chart of the systematic review process is shown in Fig. 1. PUBMED and EMBASE search identified 20 and 67 published articles related with the topic object of our review, respectively. After identification of duplicates ($n = 19$), 68 published records were preselected. One of the selected studies [35] was replaced by the most recent update of the same cohort, which incorporated a larger sample size [33]. Additionally, some publications were excluded for not meeting all the inclusion criteria: 1 case report, 35 congress communications, 13 papers not related to ABA use for RA-ILD and 9 reviews. Finally, 9 publications were included for analysis.

3.2. Study design and characteristics of RA-ILD patients

The type of study design, the main population criteria at the time of inclusion, the sample size and the outcome measures of the 9 selected studies are shown in Table 1. There were neither randomized or non-randomized trials nor meta-analysis. The oldest study was a small case series [25] and the rest of the included papers were longitudinal observational studies, mainly retrospective [26–31,33] with only one prospective study recently published [32]. ABA was the only evaluated therapy in this population of RA-ILD in 4 studies [25,28,31,33], while 4 other studies included data on therapy with ABA and other bDMARDs (TNFi, RTX, TCZ) [26,27,29,30] and one study reported data on treatment with ABA and other csDMARDs and bDMARDs [32]. The case series [25] and six of the observational cohort studies [27–29,31–33] analyzed hospital-based data, while 2 studies reported data from U.S. commercial and public insurance claims databases, MarketScan and Medicare [26,30].

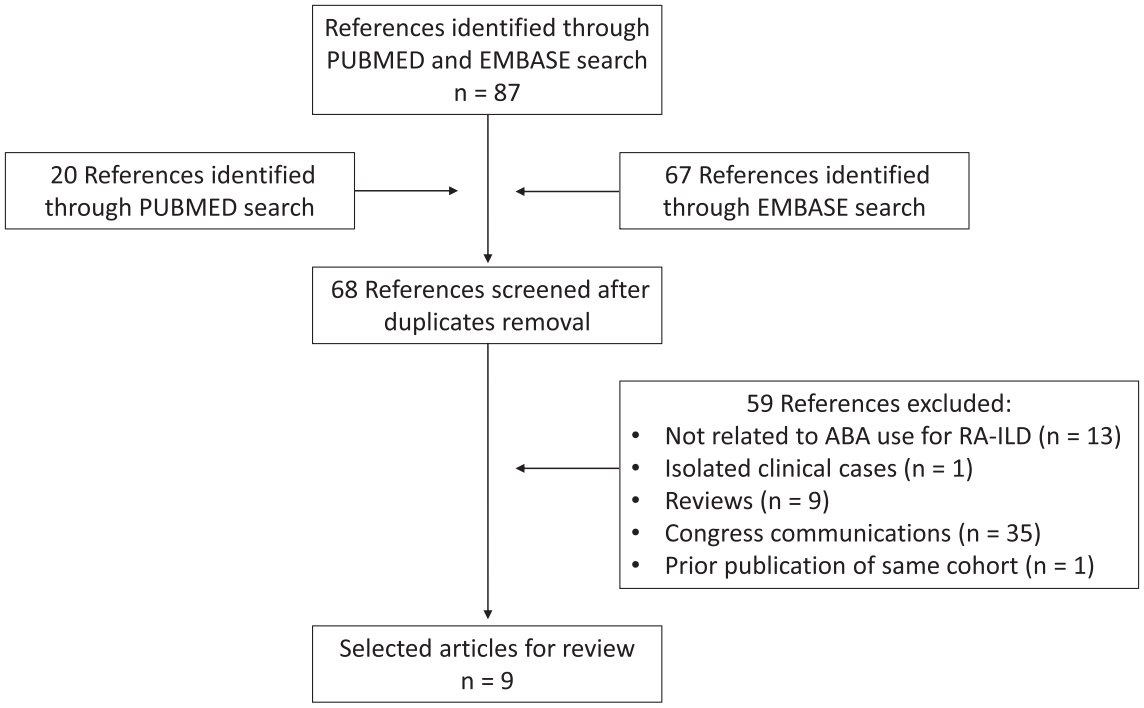

Fig. 1. Flow chart of identification and selection of studies included in this review.
Abbreviations: ABA: abatacept; RA-ILD: rheumatoid arthritis with interstitial lung disease.

The sample size of the hospital cohorts, without taking into account the case series, was low in most of them, ranging between 16 and 131 [27–29,31,32], with the exception of the recently published multicenter study from Spain that included 263 patients [33].

The main demographic and clinical characteristics of patients are summarized in Table 2. At study inclusion, mean age ranged from 61.2 to 75 years and mean duration of RA varied from 7.4 to 18 years. RA classification criteria used were the rheumatologist opinion [27], the International Classification of Diseases Ninth Revision (ICD-9) diagnosis codes of RA [26,30] and the 1987 [36] or 2010 criteria of the American College of Rheumatology/European League Against Rheumatism [37] in 6 articles [25,28,29,[31,32],33]. Subcutaneous ABA was the most frequently reported administration route (74.5% to 91%) and ABA was generally used in combination with csDMARDs (58% to 75%). First-line indication of ABA ranged from 22.8% to 64.9%.

When described, RA patients were moderately active and slightly disabled at the initiation of the study, but response of RA activity and disability was measured in 6 studies [25,27,28,31–33] using DAS28 [25,27,28,31,33], SDAI scores [27] and DI-HAQ [28], shown in Table 3. In 2 studies sera biomarkers, Krebs von den Lungen-6 (KL-6) [27,28] and matrix metalloproteinase-3 (MMP-3) [27], were also evaluated.

ILD was diagnosed by HRCT [27–29,31–33], with/without lung biopsy confirmation, or by the ILD diagnosis ICD-9 codes [26,30]. ILD was classified in different patterns according to the criteria of the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias: definite or probable UIP, NSIP, bronchiolitis obliterans (BO), organizing pneumonia (OP), and mixed patterns [38] in 3 articles [31–33]. The mean evolution of ILD ranged from 1 to 6.7 years and the most frequent ILD subtypes were UIP and NSIP ranging from 43.3% to 65.7% and from 21.4% to 50%, respectively. When described, mild to moderate ILD predominated over severe forms (Table 3).

ILD changes during evolution were analyzed by changes in dyspnea scores [33], lung function tests (LFT) [31–33] and/or HRCT [25–33]. Regarding the HRCT scoring system used, there was a great variability among studies (Table 3). Presence and change of ILD signs according to the radiologist evaluation was used in 3 articles [25,29,32,33]; a semiquantitave score from 0 to 3 taking into account the vertical extension of ILD was used in 2 studies [27,28], defining worsening and improvement as the increase or reduction of the grade of ILD; while the score by Walsh et al. [39], which takes into account the presence of reticulation, honeycombing, ground-glass opacity (GGO) and consolidation in 6 anatomic areas, was used in the study by Cassone et al. [31].

Regarding the definitions of response of the Modified Medical Research Council (MMRC) scale for dyspnea, a decrease of at least 1 point was considered improvement, an increase $\geq$1 point identified worsening, whereas stabilization was diagnosed in the absence of changes with respect to the baseline [33].

LFT outcomes most frequently included were forced vital capacity (FVC) and/or diffusion lung capacity for carbon monoxide (DLCO) [31–33]. A FVC $\geq$80% of the predicted values was considered normal [31–33], with the same cut-off point for DLCO. With regard to LFT response to ABA treatment, a change of 10% of FVC and 15% of DLCO compared to baseline values was considered clinically significant by Cassone et al. [31], while Fernández-Díaz et al. defined improvement and worsening as a change of $\geq$10% for both FVC and DLCO, in terms of increase or decrease, respectively, and stabilization when the values of the change were below that cut-off point [33]. However, Mena-Vázquez et al. defined the outcome of ILD as a combination of the evolution of LFT and imaging, considering improvement, when there was an improvement of FVC ($\geq$10%) or DLCO ($\geq$15%) and no HRCT worsening; stabilization, when there was no imaging worsening and there was stabilization or improvement of FVC or DLCO $<$10% and $<$15%, respectively; and worsening, with a decrease in FVC $>$10% or DLCO $>$15% associated with radiological worsening [32].

Some studies evaluated ILD incidence with ABA therapy, defined by the appearance of ILD signs in HRCT [26,27] or by ICD-9 codes [26], with a more specific definition that included diagnoses of post-inflammatory pulmonary fibrosis and idiopathic interstitial pneumonia in the primary claim position, and a more sensitive definition, including diagnoses of rheumatoid lung and other specified and unspecified alveolar and parietoalveolar pneumopathies in any claim position. With regard to ILD exacerbation definitions, they ranged from imaging worsening in the observational studies to proxies of ILD-related

Table 1
Main study design and outcome measures.

Author, year	Population	N	Type of study (period)	Exposure (mean)	Outcome measures
Mera-Varela, 2014	RA-ILD initiated or exacerbated after TNFi and treated with ABA	4	Case series (2008–2009)	35 months	PO: Efficacy and safety of ABA for RA-ILD
Curtis JR, 2015	2 RA cohorts, with and without ILD, treated with bDMARDs[$] as new users, with former bDMARD use	ABA cohorts: ILD–: 2683 ILD+: 109 Rest of cohorts: ILD–: 8117 ILD+: 310	MarketScan and Medicare databases (01/01/2010–06/30/2012)	0.7 years	PO (cohort without ILD): Risk of ILD incidence, global and by DMARD SO (ILD cohort): Risk of ILD-related hospitalization, global and by DMARD
Nakashita, 2016	2 RA-ILD cohorts treated with ABA or TNFi for >1 year	ABA = 16 TNFi = 46	Retrospective observational cohort (therapy initiated before March 2013)	1 year	PO: Efficacy and safety of ABA for RA-ILD patients SO: Comparison with TNFi
Kurata, 2018	RA treated with bDMARDs (ABA, TNFi or TCZ) with HRCT evolution control	49 (ABA 12, TNFi 30, TCZ 7)	Retrospective observational cohort (April 2008 – March 2017)	69.6 weeks	PO: bDMARD association with development or worsening of RA-ILD/AD SO: Factors associated with the outcome
Mochizuki, 2019	RA treated with ABA for >1 year	131	Retrospective observational cohort	47.8 months	PO: Percentage and rate of ILD deterioration SO: Factors associated with ILD deterioration
Kang[a], 2019	3 RA cohorts, with ILD, COPD or asthma, treated with ABA or TNFi as new users, naïve to both and mutually exclusive	Medicare: ABA = 420 TNFi = 1579 MarketScan: ABA = 158 TNFi = 1138	Medicare database (01/01/2008–09/30/2015) and MarketScan database (01/01/2006–09/30/2015)	1.0–1.6 years	PO: Risk of ILD, COPD or asthma exacerbations (requiring hospitalization or ED visit) SO: Individual risk of serious exacerbations requiring hospitalization; serious exacerbations requiring ED visit; non-serious exacerbations requiring outpatient visits; serious and non-serious respiratory complications
Cassone, 2020	RA-ILD treated with ABA for at least 6 months	44	Multicenter retrospective observational cohort (2012–2018)	26.5 months (median)	PO: Efficacy and safety of ABA for RA-ILD SO: Factors associated with the outcome
Mena-Vázquez, 2020	RA-ILD treated with DMARDs	70	Multicenter prospective observational cohort (2015–2017)	At least 2 years	PO: Effect of DMARDs on RA-ILD worsening
Fernández-Díaz, 2020	RA-ILD treated with at least 1 dose of ABA	263	Multicenter open-label non-controlled registry (2010–2019)	22.7 months	PO: Pulmonary efficacy and safety of ABA for RA-ILD SO: Corticosteroid-sparing dose effect, articular efficacy, and retention rate of ABA

ABA: abatacept; AD: airway disease; bDMARD: biologic disease-modifying anti-rheumatic drug; COPD: chronic obstructive pulmonary disease; ED: emergency department; DMARDs: disease-modifying anti-rheumatic drugs; HR: hazard ratio; ILD: interstitial lung disease; ILD–: cohort without ILD; ILD+: cohort with ILD; IQR: interquartile range; N: number of patients; PO: primary outcome; PY: patient-years; r: range; RA: rheumatoid arthritis; RA-ILD: rheumatoid arthritis with associated interstitial lung disease; RTX: rituximab; TCZ: tocilizumab; TNFi: TNF inhibitor. SO: Secondary outcome.

[$] bDMARDs included were: ABA, RTX, TCZ and TNFi.

[a] Data of the RA-ILD cohort.

exacerbations or complications such as hospitalizations, emergency department (ED) visits or outpatient visits related to ILD and serious and non-serious respiratory complications (respiratory infections and respiratory failure) [26,30]. In some studies, ABA risk of ILD incidence and exacerbation was compared with other DMARDs, including TNFi, RTX, TCZ or even csDMARDs [26,27,29,30,32].

3.3. Efficacy of abatacept at pulmonary level in RA-ILD patients

The data on the efficacy of ABA at the lung level in patients with RA-ILD described in the included studies are overall good after a cumulative follow-up period of 185.4 months, ranging from 12 to 47.8 months. Imaging improvement or stabilization of ILD reached values of 76.6% to 100%. Regarding LFT, DLCO showed a better response than FVC, with an improvement or stabilization of DLCO and FVC in 88.9% to 90.6% and in 86.1% to 87.7% of patients, respectively.

Regarding the published evidence, the oldest study described a small case series of 4 seropositive longstanding RA-ILD patients in their seventies, 75% female, who received ABA from 2008 to 2009 for persistent joint activity [25]. The debut of ILD (3 cases) or its exacerbation (1 case) occurred after treatment with TNFi administered between 2001 and 2004 due to insufficient response of the disease to csDMARDs and after a period of 15 to 42 months, except in one patient in whom it occurred after the 2nd dose of infliximab. The choice of ABA treatment, due to the ineffectiveness of other csDMARDs, was based on the fact that it was the only bDMARD that at that time had not yet been associated with the occurrence or exacerbation of ILD. ABA use was mainly in monotherapy, except in one patient in whom it was combined with leflunomide (LF). The authors described that all the patients presented a favorable joint response without signs of ILD progression, neither exacerbation of the respiratory symptoms nor deterioration of the respiratory function or imaging tests. There were no notable adverse events after a mean follow-up of 35 months.

Of greater scientific interest are the data provided by longitudinal studies published later on [27–29,31–33]. Nakashita et al. reported a monocentric retrospective observational study including 16 ILD-RA patients who had received at least one year of ABA treatment [27]. Mean age was 71.1 years and female sex predominated. Previous therapies were TNFi (44%) and TCZ (13%) and mean (SD) DAS28-ESR and SDAI were 4.47 (1.40) and 16.9 (11.3), respectively. HRCT involvement, quantified semi-quantitatively by the degree of vertical extension affected, was mild in 56%, moderate in 25% and severe in 10%. After one year of treatment, no patient presented worsening of ILD in the HRCT and complete resolution of the ILD was observed in two cases with mild involvement. RA activity improved and DAS28-ESR, SDAI, and glucocorticoid dose were significantly reduced. Surprisingly, KL-6 levels did not show significant changes, but levels of MMP3 were significantly reduced.

Similar good results were reported by Mochizuchi et al. [28]. Their retrospective cohort included 131 long-standing RA patients with (n = 55) and without baseline ILD (n = 76) treated with ABA for at least one year. Patients were slightly younger (67.9 years) and with more female representation (87.8%) than in previous reports, and few of them were current smokers (8.4%). ILD involvement was mainly low (24.4%) to

Table 2
Baseline demographics and clinical characteristics of patients.

Study	Age, years (mean ± SD)	Female sex (%)	Smoking (%)	RA duration (mean ± SD)	RF +/aCCP + (%)	Baseline ILD (%)	ILD duration	Previous bDMARDs/ Type	Previous csDMARDs	Pulmonary Comorbidity
Mera-Varela, 2014	72–75 (range)	75	NR	18 (16–21) years mean (range)	100/NR	100	1–6 years	100% TNFi	LF 100%	Silicosis 25%
Curtis JR[a], 2015	ILD–: 53.9 ± 12.6 ILD+: 61.2 ± 10.3	ILD–: 83 ILD+: 75.2	NR	NR	NR/NR	4.1	NR	100%/ ILD–: 69.5% TNFi ILD+: 63.3% TNFi	MTX: ILD–: 50.7% ILD+: 40.4% Others: ILD– 32.9% ILD+ 49.5%	Asthma: ILD–: 4.4% ILD+: 4.6% COPD: ILD–: 3.4% ILD+: 16.5%
Nakashita[a], 2016	71.1 ± 8.8	62.5	NR	NR	NR/NR	100	NR	44% TNFi, 13% TCZ	NR	NR
Kurata[b], 2018	64.1 ± 11.2	77.6	35 current or ever	9.45 ± 8.45 years	80.0/ 77.1	46.7	NR	NR	NR	12.2 CE%
Mochizuki, 2019	67.9 ± 10.4	87.8	8.4 current	10.7 ± 11.6 years	NR/80.9	42	NR	NR	NR	NR
Kang[a], 2019	Medicare: 73.8 ± 6.3 MarketScan: 63.4 ± 11.0	Medicare: 82.6 MarketScan: 78.5	Medicare*: 17.4 MarketScan*: 15.8	NR	NR/NR	100	NR	Naïve to bDMARDs and TOF	Medicare: MTX 46.9%, LF 31%, HOCQ 29.5% MarketScan: MTX 41.1%, LF 27.9%, HOCQ 28.5%	Hospitalized infections: Medicare: 10.7% MarketScan: 5.1%
Cassone, 2020	65 (11) median (IQR)	72.7	52.3 current or ever	89 (142) months median (IQR)	86.4/ 90.1	100	20 (58) monthsmedian (IQR)	56.8%/TNFi 43.2%, TCZ 20.5%, RTX 11.4%, JAKi 6.8%	MTX 72.3%, LF 45.5%	COPD 18.2%
Mena-Vázquez, 2020	68.8 ± 7.8	55.7	77.1 current or ever	161.0 ± 125.9 months	92/82.9	100	3.5 years	NR	70%	NR
Fernández-Díaz, 2020	64.6 ± 10.0	57.0	52.8 current or ever	9.7 ± 8.7 years	89.4/ 88.6	100	1 (0.25–3.44) year median (IQR)	47.5%/ 38.4% TNFi, 5.3% RTX, 4.6% TCZ	MTX 80.6%, LF 41.1%, HOCQ 23.2%, others 8%	NR

ABA: abatacept; AD: airway disease; aCCP+: positive anti-cyclic citrullinated peptide antibodies; AZA: azathioprine; bDMARDs: biologic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DLCO: lung diffusion capacity for carbon monoxide; RF+: positive rheumatoid factor; FVC: forced vital capacity; GS: gold salts; HOCQ: hydroxychloroquine; ILD: interstitial lung disease; ILD-: cohort without ILD; ILD+: cohort with ILD; IQR: interquartile range; JAKi: janus kinase inhibitors; MTX: methotrexate; NR: not reported; RA: rheumatoid arthritis; RTX: rituximab; SD: standard deviation; SSZ: sulfasalazine; TCZ: tocilizumab; TNFi: TNF inhibitors; TOF: tofacitinib.

[a] Data collected in this table are related to ABA cohorts.

[b] Data related to the whole cohort, including other bDMARDs.

[*] Smoking was identified by the ICD-9 diagnosis codes (305.1, 989.84, 649.0, V15.82), CPT codes (99,406, 99,407, S9075, S9453) or use of varenicline, bupropion, nicotine from the claims associated with pharmacy dispensing.

moderate (13.7%), being severe in only 3.5% of them. After a mean follow-up of 47.8 months (range: 14–85), 92.7% of the patients with baseline ILD did not show deterioration in HRCT and, in addition, 14.5% improved. ILD deterioration was observed in 4 (7.3%) of the patients with baseline ILD, 2 with grade 1 and 2 HRCT involvement, respectively, but only two patients required admission [28]. MTX use (odds ratio (OR) 12.75, 95% confidence interval (CI) 1.09–148.77) and change in KL-6 (OR 1.00, 95% CI 1.00–1.01) were significantly related to ILD worsening.

Cassone et al. published a retrospective multicenter observational study that evaluated ILD evolution of RA patients treated with ABA for at least 6 months [31]. They included 44 patients from 8 Italian centers, diagnosed between 2012 and 2018 with a mean disease duration of 89 months. Patients were younger than in previous studies (65 years) and had a relatively short ILD evolution (20 months). Most of the patients were positive for RF (86.4%) and aCCP (90.1%), 52.2% current or ever smokers and 22.7% had concomitant chronic obstructive pulmonary disease (COPD). ABA administration was mainly subcutaneous (89.9%) and in combination with csDMARDs (75%), being first-line treatment in 43.2% of patients and second-line in 34%. NSIP was the most prevalent HRCT pattern (50%), followed by UIP (43.2%) and OP (2.3%), with combined pulmonary fibrosis and emphysema (CPFE) in 4.5% of cases. Baseline FVC was normal in 82.1%, while DLCO was normal only in 50% of those with available LFT (82%). At the end of the follow-up, at 26.5 months on average, 70.4% of patients showed stability on HRCT imaging, 11.4% improved and 18.2% deteriorated. Serial LFT were available in 81.8% of patients, showing FVC and DCLO stability in 77.8% and 50%, respectively, improvement in 8.3% and 38.9%, and worsening in 13.9% and 11.1%, respectively. Authors could not identify factors associated with HRCT evolution, apart from a trend for a worst FVC evolution in male patients ($p = 0.07$).

More recently, Fernández-Díaz et al. [33] have published the largest multicenter retrospective cohort assessing the efficacy and safety of ABA in RA-ILD patients from 53 Spanish hospitals, which represents the extension of their former publication [35], including 263 patients that had received at least one dose of ABA between January 2010 and June

Table 3
Additional therapies associated with abatacept and baseline outcome variables.

Study	MTX use (%)	GC use (%)	Outcome variables	DAS28 (mean ± SD)	SDAI	HAQ	CRP (mg/dL)	HRCT score and severity	FVC (%)	DLCO (%)
Mera-Varela, 2014	0	NR	Imaging PFT	NR	NR	NR	NR	NR	NR	NR
Curtis JR, 2015	NR	ILD–: 77.3 ILD+: 80.7	ILD incidence; ILD-related hospitalizations	NR	NR	NR	NR	NR	NR	NR
Nakashita[a], 2016	NR	88	HRCT DAS28-ESR SDAI Prednisone dose KL-6/MMP3	4.47 ± 1.40 (ESR)	16.9 ± 11.3	NR	NR	Semiquantitative score (0–3) 9% grade 0, 56% grade 1, 25% grade 2, 10% grade 3	NR	NR
Kurata[b], 2018	30.6	83.7	HRCT	NR	NR	NR	2.36 ± 2.41	Presence of ILD (reticular shadow, honeycombing or GGO) or AD signs[#]	NR	NR
Mochizuki, 2019	58	48.9	HRCT KL-6	4.01 ± NR (CRP)	NR	0.84	NR	Semiquantitative score (0–3) 58% grade 0, 24.4% grade 1, 13.7% grade 2, 3.8% grade 3	NR	NR
Kang, 2019	NR	Medicare: 84.05 MarketScan: 74.7	ILD exacerbations	NR	NR	NR	NR	NR	NR	NR
Cassone, 2020	38.6	75	HRCT FVC/DLCO	NR	NR	NR	NR	Walsh score UIP 43.2%, NSIP 50%, CPFE 4.5%, OP 2.3%	88.5	66.4
Mena-Vázquez, 2020	48.4	>50	HRCT FVC/DLCO	2.9 ± 1.4	NR	0.7	5.0 (2.9–13.0) median (IQR)	Worsening defined by an increase ≥20% of extension of ILD elementary lesions UIP 65.7%, NSIP 21.4%, fibrotic NSIP 14.8%	71.9	63.3
Fernández-Díaz, 2020	17.5	NR	HRCT FVC/DLCO MMRC scale DAS28 Prednisone dose	4.5 ± 1.5	NR	NR	NR	Radiologist criteria UIP 40.3%, NSIP 31.9%, Rest 27.8%	85.9	65.7

ABA: abatacept; CPFE: combined pulmonary fibrosis and emphysema; CRP: C-reactive protein; DAS28: 28-joint disease activity score; DLCO: lung diffusion capacity for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; GC: glucocorticoids; GGO: ground-glass opacity; HAQ: Health Assessment Questionnaire; HRCT: chest high resolution computerized tomography; ILD: interstitial lung disease; ILD-: cohort without ILD; ILD+: cohort with ILD; MMRC: modified Medical Research Council score for dyspnea; MTX: methotrexate; NR: not reported; NSIP: non-specified interstitial pneumonia; OP: organized pneumonia; SD: standard deviation; SDAI: simplified disease activity index; UIP: usual interstitial pneumonia.

[a] Data collected in this table are related to ABA cohorts.

[b] Data related to the whole cohort.

[#] AD signs: thickened bronchial walls, bronchiolitis, bronchodilation and mucoid impaction.

2019. Patients included, with a mean age of 65 years, were predominantly RF and aCCP positive and had an active long-standing and erosive (57%) disease, with a rate of current or ever smokers of 52.8%. ABA was the first-line bDMARD in 60 patients and subcutaneous administration (74.5%) and use in combination with csDMARDs (57.8%) predominated. The relatively short evolution of ILD, median of 1 year, at ABA initiation is one of the points to highlight of this study, as well as its symptomatic nature, as HRCT was indicated on the grounds of respiratory clinic in most of them and related to alterations on LFT in the remaining 28.8%. The most frequent respiratory profile was of patients with UIP or NSIP (72%), mild to moderate dyspnea (58%), normal FVC and slightly reduced DLCO. Furthermore, in 11.4% of patients, ILD was considered to be associated with the use of csDMARDs (MTX and LF, $n = 11$ and $n = 1$, respectively) or bDMARDs (TNFi, $n = 14$). ILD stabilized or improved in most of them after 12 months of treatment, as reflected by the evolution of dyspnea score (in 91.9%), FVC (in 87.7%), DLCO (in 90.6%) and chest HRCT (in 76.6%).

3.4. Role of the combination of methotrexate

Regarding the combination of ABA with MTX, results are discordant. Mochizuki et al. advised against it, as they found that MTX use was a factor significantly associated with ILD deterioration (OR 12.75, 95% CI 1.09–148.77) [28]. However, this study was conducted in Japanese RA patients and other studies conducted in Caucasian RA patients indicate that the use of MTX in combination with ABA may be a safe strategy. In this regard, Cassone et al. did not find differences regarding worsening, stability, or improvement of ILD involvement in HRCT in relation to the use of MTX in combination with ABA [31]. In the same line, Mena-Vázquez et al. [32] did not find relationship between MTX therapy and ILD evolution and Curtis et al. [26] found that recent exposure to MTX seemed to reduce the risk of ILD-related hospitalizations (hazard ratio (HR) 0.16; 95% CI 0.06–0.46; $p = 0.0007$). Moreover, Fernández-Díaz et al. [40] found that patients who had received MTX plus ABA had significantly further decrease the dose of prednisone when compared with those using ABA alone.

3.5. Role of the ILD pattern

Cassone et al. could not find an association between the HRCT lung pattern and the efficacy of ABA, although improvement was numerically more frequent in NSIP patients and deterioration in UIP patients. While 6 patients with UIP deteriorated and one improved, only 2 patients with NSIP showed image worsening and 4 experienced improvement, with stabilization of 12 and 16 patients with UIP an NSIP, respectively [31]. However, Kurata et al. found no relationship between different imaging signs of ILD such as GGO, honeycombing or reticular shadow and the evolution of ILD with ABA therapy [29] and Mena-Vázquez et al. found

no association between the radiological ILD pattern and the progression of lung disease [32]. With a higher sample size, Fernández-Díaz et al. found a favorable response from dyspnea, LFT and HRCT with ABA treatment as well as an improvement of DAS28 and a reduction of the prednisone dose regardless of the type of HRCT pattern [41], supporting ABA therapy in all the ILD scenarios.

3.6. Comparison of abatacept with other DMARDs

Attempts to establish comparison between ABA and the rest of bDMARDs or csDMARDs have been made. Nakashita et al. compared the efficacy findings of the ABA cohort with another cohort of 46 patients of the same center who had similar baseline characteristics of RA-ILD and who were treated with TNFi [27]. In the latter, 30% presented worsening of ILD versus none of the ABA cohort, and in 7 cases TNFi were changed to ABA, either due to worsening of ILD or due to an increase in KL-6 levels.

A prospective multicenter study assessing RA-ILD evolution after 2 years of treatment with different csDMARDs and bDMARDs has recently been published [32]. The population included 70 patients on their seventies, balanced between men and women, mainly seropositive and two-thirds were ever smokers. Half of the patients (58.6%) received only csDMARDs, 32.9% were on a combination of csDMARDs and bDMARDs and only 5.7% were taking bDMARDs in monotherapy. To note, 19% of the patients had received a bDMARD for a median of 24 months prior to the baseline visit. At inclusion, patients had a mean ILD evolution of 3.5 years and UIP was the most frequent HRCT pattern (65.7%), followed by NSIP (21.4%) and fibrotic NSIP (14.8%). Although the mean FVC and DLCO significantly deteriorated at the end of follow-up, only 30.4% of the patients experienced HRCT worsening of ILD and only one patient died as a consequence of lung deterioration and infection. Globally, improvement was observed in 11.4% of patients, stabilization in 57.1% and deterioration in 30%. Focusing specifically on ABA, 8 patients received this therapy during the whole period of the study and none experienced ILD deterioration. Furthermore, non-TNFi bDMARDs (ABA, RTX and TCZ, in that order) were associated with a 90% reduction in the relative risk (RR) of deterioration of ILD at 24 months of follow-up [32].

3.7. Abatacept effect on RA joint disease

Coverage of this important aspect of the disease was generally scarce. Two studies just mentioned a favorable evolution of joint involvement at the end of follow-up, without providing objective data [25] or concluding that remission or low activity had been reached in all patients except 3 [31]. Nevertheless, 3 studies reported validated scores of RA activity as DAS28 or SDAI, with numerical [32] or significant improvement [27,33] and reduction of prednisone dose [27,33].

3.8. Abatacept safety

Regarding safety of ABA in RA-ILD patients, some studies have described the type and frequency of adverse events (AE), while others have focused on the risk of ILD incidence and exacerbation with ABA, establishing comparisons with other DMARDs.

3.8.1. Abatacept risk of incidence or exacerbation of ILD in RA patients

The accumulated evidence on the safety profile of ABA with respect to the risk of incidence or exacerbation of ILD in patients with RA is reassuring. Mochizuki et al. [28] reported a deterioration rate of ILD of 0.02 patient-years with ABA after a mean follow-up of 47.8 months, but the analysis of the subgroup of patients with normal baseline HRCT ($n = 76$) only identified 7 patients with new onset ILD, being MTX use and KL-6 change the significant risk factors associated with ILD deterioration in their series of Japanese patients.

Curtis et al. evaluated ILD incidence and exacerbation rates in RA patients treated with different bDMARDS (ABA, RTX, TCZ and TNFi). All included patients had a history of prior use of bDMARDs to select cases with a more refractory disease [26]. In the ABA cohort, the frequency of a new ILD diagnosis ranged from 0.1% to 0.4% and the unadjusted ILD incidence rate ranged from 1.1 (95% CI 0.1–0.4) to 4.0 (95% CI 1.6–8.2) per 1000 person-years (PY), when using the most specific or the most sensitive ILD definition, respectively. Although no statistically significant difference among the bDMARDs evaluated was found, when using the most sensitive definition of ILD, ABA cohort showed the lower incidence rate, while infliximab rate was the highest (12.2 per 1000 PY; 95% CI 5.6–23.2). Age $\geq$ 65 years (HR 3.54; 95% CI 2.07–6.03; $p < 0.0001$), male sex (HR 3.09; 95% CI 1.14–8.35; $p = 0.0258$) and other pulmonary comorbidities (HR 4.83; 95% CI 1.71–13.68; $p = 0.0030$), and marginally, recent exposure to glucocorticoids (HR 1.99; 95% CI 0.98–4.06; $p = 0.0586$) were the risk factors associated with ILD incidence [26]. Regarding ILD-related exacerbations, identified by the hospitalizations with a primary diagnosis of ILD, pneumonia or lung transplant, these complications occurred in 4.1% to 8.4% of patients and the unadjusted ILD-related hospitalization rate with ABA (96.5 per 1000 PY; 95% CI 38.8–198.7) was lower than TNFi (111.9 per 1000 PY; 95% CI 65.2–179.1) and RTX (234.2 per 1000 PY; 95% CI 133.8–380.3) rates, although it did not reach statistical significance. Male sex (HR 2.47; 95% CI 1.28–4.78; $p = 0.0073$) and prior hospitalizations due to asthma (HR 3.42; 95% CI 1.19–9.82; $p = 0.0224$) or ILD/pneumonia (HR 2.28; 95% CI 1.11–4.67; $p = 0.0245$) were significantly associated with an increased risk of hospitalization, while recent MTX exposure seemed to reduce the risk (HR 0.16; 95% CI 0.06–0.46; $p = 0.0007$).

The retrospective observational study by Kurata et al. [29] assessed the association between the administration of different bDMARDs (ABA, TNFi and TCZ) and the occurrence or exacerbation of airway disease (AD) and/or ILD in patients with RA. Forty-nine patients were included, mainly women (77.6%) in their sixties with active seropositive and long-standing RA. TNFi was the most widely used bDMARD (61.2%), followed by intravenous or subcutaneous ABA (24.5%) and TCZ (14.3%), in combination with csDMARD in all patients (30.6% methotrexate) and prednisolone in 83.7%. ILD evolution was classified in two categories: a) improvement or stability and b) deterioration or new onset ILD. Prior to bDMARDs start, serial HRCT monitoring had been done in 49% of patients, without significant changes in the follow-up in 75% of them, but with signs of AD and/or ILD progression in the remaining 25%. New onset ILD occurred in 3 patients (11.5%), 2 with baseline AD and 1 without prior lung disease (11.5%), after a mean follow-up of 69.6 weeks. Baseline ILD was seen in 46.7% ($n = 23$) of patients, with concomitant AD in 12.2%. Among them, 30.4% showed deterioration on imaging (2 of them had concomitant AD), while 52.2% remained stable and 17.4% improved, after a mean follow-up of 69.6 weeks. Pre-existing AD revealed as a significant independent risk factor for emergence or exacerbation of ILD (OR 7.40, 95% CI 1.28–42.8), while ABA use yielded a significant protective role (OR 0.07, 95% CI 0.01–0.99).

Kang et al. evaluated the risk of pulmonary exacerbations in 3 cohorts of RA patients with ILD, COPD or asthma, selecting these primary codes in each cohort to define exacerbations, respectively [30]. In this study, new users of ABA or TNFi were selected to reduce confounding by indication at baseline and immortal time bias. Focusing on the ILD cohort, composite pulmonary exacerbations (including hospitalizations or ED visits) occurred frequently with both ABA (incidence rate (IR) of 6.32 and 3.59 per 100 PY) and TNFi (IR of 8.59 and 11.8 per 100 PY) in Medicare and MarketScan datasets, respectively, although they were numerically higher for TNFi. Despite the incidence rate ratio (IRR) of ILD exacerbations favored ABA versus TNFi, 0.44 (95% CI 0.18–1.09), it was not statistically significant. A similar favorable tendency was found when IRR of individual components of the composite pulmonary exacerbations such as hospitalizations (0.53, 95% CI 0.39–0.72) and ED visits (0.51, 95% CI 0.24–1.10), as well as ambulatory exacerbations (0.93, 95% CI 0.77–1.12) and serious and non-serious respiratory complications (0.71, 95% CI 0.59–0.86 and 0.93, 95% CI 0.69–1.26, respectively) were estimated.

3.8.2. Other adverse events

Few studies describe AE in detail, but no unexpected warning signs were detected. In a case series of 4 RA-ILD patients, the authors just pointed out that there were no remarkable side effects during the mean follow-up of 35 months [25] and Kurata et al. [29] described 6 cases of infectious pneumonia in 2 patients without lung involvement, 3 patients with AD and only one with ILD, leading to AD and ILD exacerbations, respectively, without specifying the type of bDMARD used by those patients. All of them solved with antibiotic therapy and temporal halting of the bDMARDs, which were resumed afterwards in 5 of the patients. Cassone et al. [31] reported just 4 withdrawals among the 44 patients included in the study, 3 due to loss of efficacy and one related to a non-respiratory infection. Mena-Vázquez et al. [32] reported an AE rate of 42.9%, being mild in 25.7% and severe in 17.1%. Both mild and severe AE were mainly the result of respiratory infections (21.4% and 12.8%, respectively), with one death due to ILD worsening and lung infection in a patient treated with RTX in combination with LF. Fernández-Díaz et al. reported an ABA retention rate of 76.4% at the end of follow-up, after a mean of 22.7 months, and a serious AE rate of 10.6%, mainly respiratory infections (9.5%) [33]. In this cohort, 3 patients developed cancer during follow-up (2 lung cancer and 1 germ cells tumor) and 6 patients died due to ischemic heart disease ($n = 3$), ILD deterioration ($n = 2$) and severe respiratory infection ($n = 1$). Both cases of ILD worsening occurred 2 and 3 months after ABA withdrawal due to articular inefficacy and major surgery, which led to multiple non-infectious complications that prevented the reintroduction of ABA [33].

4. Discussion

The therapeutic armamentarium available for RA has undergone a revolution in recent years with the emergence of biological therapies and, more recently, oral small molecules. Its innovative mechanisms of action, directed against specific molecular or cellular targets involved in the pathogenesis of the disease, brings us closer to the possibility of personalized medicine for RA. However, at the present time, we lack biomarkers that allow us to choose the most specific treatment for each individual patient or to clearly establish which is the best therapeutic alternative after failure of the first DMARD, in many cases [42,43]. In this context, among the parameters to be considered in making this choice, factors such as comorbidity derived from cardiovascular risk [44] or the existence of extra-articular manifestations such as ILD may be of particular relevance. Knowledge about the pathogenesis and evolution of ILD in RA has advanced considerably in recent years. However, there are still many aspects that require further investigation. One of the main questions to be answered is that related to its treatment, given the paradox that DMARDs with a theoretical potential to exert a beneficial effect on the evolutionary course of RA-ILD have also been associated with a potential capacity to trigger or exacerbate this disease. This is the main reason for this review that seeks to elucidate the usefulness of ABA to treat RA-ILD patients, since this drug has shown an especially favorable safety profile both in clinical trials and in real-world studies of RA [22,23,45] and has presented encouraging beneficial results in mouse animal models of lung fibrosis or hypersensitive pneumonitis, preventing fibrosis or inhibiting lung inflammation [46–48].

The accumulated evidence to date about the role of ABA therapy for RA-ILD postulates it as an effective and safe therapeutic alternative. Imaging improvement or stabilization happened in 76.6% to 92.7% of the patients after a mean follow-up of 17.4 to 47.8 months, with a low rate of worsening and without identifying any unexpected AE. Lung functionality, in terms of dyspnea and LFT, had also a favorable response with FVC and DLCO improvement or stabilization in >85% of patients and a greater percentage of improvement of DLCO versus FVC. And all this occurred regardless of the pattern of lung involvement [29], although numerically higher improvement rates were seen in patients with NSIP than in those with UIP [31]. However, recent data from the Spanish multicenter registry presented at the last EULAR congress showed a favorable response irrespective of the pulmonary pattern [41], in agreement with the findings published by Rojas-Serrano et al. in whose study the UIP definite pattern in HRCT was not associated to a worse survival [49]. To highlight, the pulmonary results were more favorable in the cases in which the ILD evolution was shorter, from 12 to 20 months [31,33], compared to those with a longer evolution of about 3.5 years [32]. When available, LFT also identified a relatively early ILD profile as baseline FVC was normal and DLCO was only slightly reduced in most cases. This evidence suggests that treating ILD at an early stage, yet to be defined, could have a more beneficial effect, but it also supports not depriving patients with more advanced or potentially aggressive forms of ILD from treatment as they can also improve or stabilize.

On the other hand, the characteristics of the patients included in the analyzed studies reinforce the value of the good results of ABA, since they are representative of the population at risk that we have to treat in clinical practice, as most of them were longstanding RA patients, with a high mean age, predominantly RF and aCCP positive, with UIP or NSIP patterns (>70%) and mostly symptomatic at respiratory level, as HRCT tended to be indicated on clinical grounds. Of interest, good pulmonary response with ABA therapy was also observed in RA-ILD patients in whom the onset of ILD occurred in close proximity to the initiation of other treatments with csDMARDs (mainly MTX) or bDMARDs (TNFi, most frequently) and it was thought to be drug-induced.

Comparisons with other DMARDs, though scarce, show interesting results. ABA conferred significantly lower ILD worsening rates than TNFi [27]. It was also associated with a 90% reduction in the relative risk (RR) of deterioration of ILD at 24 months of follow-up compared to TNFi and csDMARDs, showing a better profile than RTX and TCZ [32].

Regarding the use of ABA in monotherapy or combined with csDMARDs in RA-ILD, and although data are still weak to draw firm conclusions due to the discrepancies, the preliminary evidence seems to be in favor of using ABA combined with csDMARDs. Only data from the Japanese population advise against the use of MTX or recommend withdrawing MTX after reaching the therapeutic goal of lung improvement or stabilization, since it was found that in Japanese RA patients MTX behaved as an independent risk factor for worsening ILD [28]. In this regard, it has been postulated that the Japanese population could have a greater genetic susceptibility to developing MTX-induced pneumonitis than other races, and an association with HLA-A*31: 01 has even been identified, with these findings not being replicated in the British population [50,51]. In contrast, the rest of the studies analyzing this issue describe MTX exposure as associated with clinical benefits such as a reduction of the dose of prednisone [40] or the risk of ILD-related hospitalizations [26], or at least not interfering with the pulmonary outcome [31,32]. This is in line with published evidence about MTX in RA-ILD. The risk of MTX-induced pneumonitis has been reported in literature (relative risk (RR) 7.81, 95% CI 1.76–34.72) especially in the first year after the treatment is started [11,52], with an incidence (3.775 per 1000 cases) superior to that described for RA-associated ILD (1.056 per 1000 cases) [53] and with an increased risk at a higher age [54]. But more recent research yields much lower figures, around 0.43% to 0.28% [55]. On the other hand, MTX has also been associated with an increased risk of respiratory infection (RR 1.11, 95% CI 1.02–1.21), which is recognized as a potential trigger for ILD [11]. However, although it remains a subject of intense debate, the evidence against MTX as a causal role in RA-ILD is increasing. With respect to this, in a meta-analysis by Conway et al. [11], MTX was not associated with an increased risk of death due to lung disease (RR 1.53, 95% CI 0.46–5.01) or non-infectious lung AE (RR 1.02, 95% CI 0.65–1.60). Detorakis et al. [56] in a case-control study found a negative correlation between MTX dose and ILD extent score at one-year and Rojas-Serrano et al. [49] found that MTX was associated with survival (HR 0.13, 95% CI 0.02–0.64). Interestingly, two recent studies have shown that MTX exposure was associated with a significantly reduced risk of incident RA-ILD and a longer time to ILD diagnosis. In a British multicenter prospective study of two early RA inception cohort studies, the early RA

study (ERAS) and the early RA network (ERAN), those OR were 0.48 (95% CI 0.3–0.79, $p = 0.004$) and 0.41 (95% CI 0.23–0.75, p = 0.004), respectively, confirming that risk factors for developing RA-ILD were higher age at the onset of RA, smoking (current or past), male gender, rheumatoid nodules and delay in appropriate treatment [57]. The same findings have been shown in an international case-control study, with an inverse relationship between MTX exposure and RA-ILD (OR 0.43; 95% CI 0.26–0.69; $p = 0.0006$) as well as a significant delay in ILD detection in MTX ever users in comparison with never users (11.4 ± 10.4 years and 4.0 ± 7.4 years, respectively; $p < 0.001$) [16].

No mention has been made of warning signs with LF, the other csDMARD frequently used in combination with ABA in the studies analyzed, even surpassing MTX in some of them, because no disaggregated efficacy or safety data is presented in any study, so we cannot comment deeply on this. As with MTX, LF-induced ILD is infrequent in the Western population (<0.1%) [12]. Although Suissa et al. [58] reported an almost 2-fold increase in the risk of ILD with LF (RR 1.9, 95% CI 1.1–3.6) in a nested case–control study, it only occurred in patients previously treated with MTX or with prior ILD and not in those without previous ILD diagnosis, suggesting a channeling bias since those patients were twice as likely to receive LF instead of MTX. Conway et al. [59] found no association of LF with infectious pulmonary AEs or increased risk of lung-related death, while it was associated with a decreased risk of non-infectious respiratory AEs (RR 0.64, 95% CI 0.41–0.97). Conversely, LF-induced ILD is more frequent in the Japanese population (1.2%), where it has been associated with a possible genetic susceptibility, the presence of previous ILD, smoking, low body weight or the use of loading dose [60]. In summary, taking together all these considerations, we feel that the use of ABA in combination with csDMARDs as MTX or LF may constitute an efficacious and safe therapeutic strategy in RA-ILD patients.

Unlike other csDMARDs and bDMARDs, communications linking ABA and the onset of pneumonitis are very rare. Wada et al. [61] reported a case of RA-ILD exacerbation two days after ABA administration, in the context of a phase III trial of ABA in Japan, that responded to glucocorticoid therapy and Dogu et al. [62] reported the acute respiratory failure of a long-standing RA patient after 2 doses of ABA. The patient developed bilateral diffuse infiltrates that initially responded to high dose glucocorticoids but died because of sepsis three weeks later. Although the authors related the use of ABA to this lung outcome, they recognized that other causative possibilities such as a flare-up of RA, an infectious trigger or the discontinuation of a previous DMARD could not be excluded. No further security alerts have been published despite the increasing use of ABA in RA-ILD patients in recent years.

Regarding the risk of ILD incidence and ILD-exacerbations in patients with RA, it seems very unlikely that ABA confers an increased risk when compared with other bDMARDs, as suggested by the results from the studies by Curtis [26] and Kang [30], as the IR and the IRR of ILD exacerbation requiring hospitalization or attendance at ED were numerically lower for ABA than for TNFi and other non-TNFi bDMARDs such as RTX or TCZ, in accordance with previous experience from post-marketing surveillance and clinical trials. The incidence of ILD in RA patients found in the pooled analysis of safety data from 8 intravenous ABA clinical trials, including 4149 patients with a cumulative exposure of 12,132 patient-years, is also very low both in the short term, since only 2 patients developed ILD (0.1%) with an IR of 0.09 (95% CI 0.01–0.31), as in the long-term with the appearance of ILD in 11 patients (0.3%) in the extension periods, with an IR of 0.11 (95% CI 0.06–0.20). Also, in post-marketing surveillance studies carried out in Japan, the ILD-incidence for ABA (0.3% for 24 weeks) was the lowest when compared with infliximab (0.5% for 6 months), etanercept (0.6% for 24 weeks), adalimumab (0.5% for 28 weeks) or tocilizumab (0.5% for 28 weeks) [22,63–66].

Besides the aforementioned, the data on the efficacy and safety of other bDMARDs in RA-ILD are helping to clarify the selection of the best therapeutic alternative in these patients. Although some studies have not identified a significant increase of risk of ILD incidence or exacerbation with TNFi when compared to non-TNFi bDMARDs [26,67] or even have found a beneficial effect of TNFi on RA-ILD [56], evidence against their use in this population is increasing. A high percentage of the reported ILD cases linked to bDMARDs has been related to TNFi [68,69], which have also been associated with numerically higher, though not significant, rates of mortality in RA-ILD than csDMARDs (21% versus 7%) in the British Registry [13], as well as higher ILD-related AE and ILD-related mortality rates than ABA or RTX [69,70]. In all these studies, previous ILD was a strong predictor of pulmonary AE or mortality with TNFi therapy.

TCZ has been associated in literature with the induction of OP in RA-ILD patients [71] or acute ILD exacerbation [72], which was linked to higher disease activity [73]. However, in other studies TCZ has shown a good safety profile and efficacy with ILD incidence rates and hospitalization rates numerically lower than TNFi [26], lung function stabilization or improvement in 76% of patients and HRCT stabilization in 25 of the 28 patients included in the multicenter study by Manfredi et al. [18], with one case of improvement and only 2 cases of deterioration.

Evidence about efficacy and safety of RTX in RA-ILD also seems to be promising. Lung parameters improved or stabilized between 68% and 76.5% of patients [74–77] and RTX exposure resulted in a lower risk of functional respiratory impairment compared with non-exposure to RTX (HR 0.51, 95% CI 0.31–0.85) [78]. Furthermore, RA-ILD patients who received RTX therapy had lower mortality rates than those treated with TNFi, nearly halved (HR 0.53, 95% CI 0.26–1.10), though the difference was not statistically significant [70]. Progression of RA-ILD was associated with UIP pattern and a baseline DLCO <46% [74], supporting early treatment as occurred in ABA studies. But, as to date there are no direct comparisons between ABA and the rest of the bDMARDs, we must be cautious when interpreting these results, although the evidence may place ABA in a position of apparent advantage in RA-ILD patients. However, the available data on the use of ABA in CTD-associated ILD, such as systemic sclerosis, inflammatory myopathies or Sjögren's syndrome, is scarcer than with RTX or TCZ, which appear to be associated with a stabilization of FVC, DLCO and HRCT [79–81].

Regarding safety, the studies did not identify any unexpected AE, showing a good safety profile of ABA according to the evidence from the integrated analysis of the short-term clinical trial program and cumulative treatment periods [23,45]. ABA maintenance rate of 76.4% is in accordance with indirect comparisons from meta-analysis showing that ABA is associated with a significantly lower risk of serious infections and AE compared to most other bDMARDs, with lesser withdrawals due to AE [82]. This safety profile is a strong argument in favor of the use of ABA in these patients with RA-ILD, due to the fact that infections are associated with a risk of pulmonary adverse outcome.

An interesting aspect to highlight that the analyzed studies suggest is the possible referral of patients with RA-ILD and greater comorbidity to receive treatment with ABA and other non-TNFi bDMARDs, based on their best preliminary efficacy and safety profile. For instance, the proportion of first-line ABA use reached up to 65% [28] and ABA, TCZ and RTX were more likely chosen than TNFi (9.2%, 10.6% and 9.9% versus 7.5%; $p < 0.05$) in patients with pulmonary comorbidities as asthma, COPD or previous pneumonia [26,30]. Recent examples of this channeling in clinical practice presented at the EULAR 2020 congress showed that despite the fact that TNFi was the most widely used bDMARD in 2 cohorts of RA-ILD from Spain and the United States as a first-line option before the diagnosis of ILD, the therapeutic strategy changed after the appearance of ILD, with ABA and RTX being the DMARDs most frequently used, respectively [83].

We can think that in the treatment of patients with RA-ILD, due to the complexity of its management and its potential severity, doctors have anticipated to incorporate the evidence shown in the literature as well as that presented in scientific conferences into their clinical practice. It has occurred before clinical practice guidelines have been developed, which we believe are urgent in this pathology. With respect

to this, although at present there is no EULAR or ACR consensus on the treatment protocol of RA-ILD patients, the usefulness of ABA treatment is beginning to be recognized by some scientific societies. The Spanish Society of Rheumatology, in its Clinical Practice Guide for the Management of Patients with RA (GUIPCAR) that was updated in 2018, recommends using ABA as a safer option (Grade C recommendation) in patients with RA-ILD who require biological treatment, and rituximab (Grade D recommendation) as an alternative [84]. Furthermore, the British Society for Rheumatology bDMARDs safety guidelines in inflammatory arthritis recommends that RTX or ABA may be considered first-line biologics in patients with ILD (grade 2C, strength of agreement (SOA) 84%) [85].

5. Limitations

This review has limitations derived from various factors. The samples are small in size in most studies and are not randomized. The follow-up time is generally short, around 12 months, although in some studies it goes up to 47.8 months, which may limit the identification of drug-induced AE. However, we believe that the assessment of the risk of inducing or exacerbating ILD may not be very affected since it has been described that it usually occurs in the first 20 weeks after the start of treatment [12]. We cannot rule out biases such as publication, since favorable results tend to be reported more frequently, or a trend to channel patients towards potentially safer therapeutic strategies, or even those derived from confounding factors that may not have been fully adjusted, like the heterogeneity of the populations of MarketScan and Medicare databases [26,30]. The results obtained from the analysis of these databases can also be affected by misclassification, as they rely on diagnosis codes for assessment of the outcomes. Racial influences on the results cannot be excluded as several studies come from Japan. However, that fact could reinforce the security of ABA as Japanese population has a potentially higher risk of ILD drug-induced side effects. Finally, there is a lack of high-quality evidence because there are no published randomized controlled studies of ABA nor head-to-head randomized comparisons that allow firm conclusions to be drawn about the role of ABA in patients with RA-ILD compared to other DMARDs. However, there is a small clinical trial underway on the role of ABA in RA-ILD patients, the APRIL (AbatacePt in Rheumatoid Arthritis-ILD) trial [86], with the aim of evaluating the feasibility of subsequently conducting a larger randomized controlled trial. The changes in FVC at 24 weeks after treating 30 patients with RA-ILD with ABA will be analyzed. Undoubtedly, these data will be of great interest to clarify the role of ABA in the treatment of these patients.

6. Conclusions

In summary, ILD is a potentially life-threatening extra-articular manifestation of RA that deserves an early multidisciplinary therapeutic management. Choosing the most appropriate DMARD for each patient at each stage of evolution remains a challenge for rheumatologists. However, and in the absence of randomized controlled studies, current evidence points to the choice of ABA as a plausible alternative to treat patients with RA-ILD who require biological therapy.

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