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ORIGINAL RESEARCH

Association between type I interferon pathway activation and clinical outcomes in rheumatic and musculoskeletal diseases: a systematic literature review informing EULAR points to consider

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ABSTRACT

Background Type I interferons (IFN-I) contribute to a broad range of rheumatic and musculoskeletal diseases (RMDs). Compelling evidence suggests that the measurement of IFN-I pathway activation may have clinical value. Although several IFN-I pathway assays have been proposed, the exact clinical applications are unclear. We summarise the evidence on the potential clinical utility of assays measuring IFN-I pathway activation.

Methods A systematic literature review was conducted across three databases to evaluate the use of IFN-I assays in diagnosis and monitor disease activity, prognosis, response to treatment and responsiveness to change in several RMDs.

Results Of 366 screened, 276 studies were selected that reported the use of assays reflecting IFN-I pathway activation for disease diagnosis (n=188), assessment of disease activity (n=122), prognosis (n=20), response to treatment (n=23) and assay responsiveness (n=59). Immunoassays, quantitative PCR (qPCR) and microarrays were reported most frequently, while systemic lupus erythematosus (SLE), rheumatoid arthritis, myositis, systemic sclerosis and primary Sjögren's syndrome were the most studied RMDs. The literature demonstrated significant heterogeneity in techniques, analytical conditions, risk of bias and application in diseases. Inadequate study designs and technical heterogeneity were the main limitations. IFN-I pathway activation was associated with disease activity and flare occurrence in SLE, but their incremental value was uncertain. IFN-I pathway activation may predict response to IFN-I targeting therapies and may predict response to different treatments.

Conclusions Evidence indicates potential clinical value of assays measuring IFN-I pathway activation in several RMDs, but assay harmonisation and clinical validation are urged. This review informs the EULAR points to consider for the measurement and reporting of IFN-I pathway assays.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The type I interferon (IFN-I) activation pathway has been related to a number of rheumatic and musculoskeletal diseases (RMDs), but the optimal assays for detection and clinical applications are unclear.

WHAT THIS STUDY ADDS

⇒ This systematic review revealed significant heterogeneity in IFN-I evidence in RMDs in terms of clinical applications (diagnosis, measurement of disease activity, prognosis, prediction of response and assay responsiveness) that may account for the lack of transition of IFN-I assays into clinical practice.

⇒ Immunoassays, quantitative PCR and microarrays were reported most frequently, while systemic lupus erythematosus (SLE), rheumatoid arthritis, myositis, systemic sclerosis and primary Sjögren's syndrome were the most studied RMDs.

⇒ IFN-I pathway activation was associated with disease activity and flare occurrence in SLE, although in most contexts the added value to existing instruments in clinical care needs to be determined.

⇒ IFN-I assays can predict response to IFN-I targeting drugs and may also predict response to other classes of therapies.

INTRODUCTION

Type I interferons (IFN-I) are cytokines with well-known antiviral and immunomodulatory activities, involved in both innate and adaptive

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Assays measuring IFN-I pathway activation show considerable promise to improve the management of RMDs, guiding clinical decisions along the whole therapeutic process. We demonstrate where harmonisation of assay methods, improved study designs and clinical validation studies are required to realise this potential.

⇒ This review informs the EULAR points to consider for the measurement, reporting and application of IFN-I pathway activation assays in clinical and research practice, which may also be of interest beyond the field of rheumatology.

responses.[1] Aberrant IFN-I production, signalling or altered regulation has been observed in a wide range of rheumatic and musculoskeletal diseases (RMDs).[2–4] Moreover, preclinical research has provided mechanistic insights for IFN-I pathway activation in RMD pathogenesis. Furthermore, drugs targeting different components of the IFN-I pathway have been licensed for systemic lupus erythematosus (SLE) and thereby support the pathogenic role of IFN-I in autoimmunity.[4]

The identification of biomarkers to improve clinical management is an important area in the field of rheumatology. However, the contribution of IFN-I pathway activation assays as biomarkers in this setting remains unclear. In this regard, it is important to note that different assays, which measure different molecules reflecting distinct aspects and components of the IFN-I pathway activation, or different IFN-I family members have been proposed. Several IFN-I pathway activation assays have been reported to correlate with clinical features across RMDs. As such, there is a substantial body of evidence suggesting a role for IFN-I in disease diagnosis, prognosis, monitoring and prediction of response. Despite this potential, the translation of assays evaluating IFN-I pathway activation into clinical practice has been rare.

Under these circumstances, and due to the relevance for RMD management, a EULAR Task Force was convened to address this unmet need. The aim of the present study was to perform a comprehensive systematic literature review (SLR) to appraise the existing literature about the potential clinical relevance of IFN-I pathway assays in RMDs to develop points to consider.

MATERIAL AND METHODS

This SLR was performed in accordance with the EULAR standardised operating procedures for EULAR-endorsed projects.[5] A multidisciplinary task force of 17 members (from 8 EULAR countries and the USA), with different backgrounds including rheumatologists, medical immunologists, virologists, translational researchers and experts in interferonopathies was formed. The task force outlined the scope of the literature search and identified six topics about the use and reporting of IFN-I pathway assays in RMDs. The first research question was focused on assay methodology (properties and classification) and it was published as a separate SLR.[6] The remaining five research questions concerned the association with clinical outcomes and were formulated under the Population, Intervention, Comparator, Outcome (PICO) framework (online supplemental text 1) for the purpose of this SLR.

Search strategy

A search strategy (online supplemental texts 2–4) was developed based on the predefined PICO and implemented in Ovid Medline, Embase and Web of Science on 31 October 2019, with the support of an experienced librarian. Titles and abstracts, followed by full-text screening was performed by two reviewers (AB and JR-C). The agreement between reviewers was high (>95%), and discrepancies were resolved by discussion or consultation with the convenor (EV).

Inclusion and exclusion criteria

Papers were included in the SLR by a two-step process. First, articles were selected if they report an assay to measure IFN-I pathway activation, according to predefined inclusion and exclusion criteria (online supplemental text 5). Next, these papers were further screened for specific eligibility criteria related to the associations with clinical outcomes (diagnosis, disease activity, prognosis, response to treatment and assay responsiveness/change over time) in RMDs (online supplementary text 6).

Data extraction and synthesis

Data from the included studies were extracted using a standardised template. The risk of bias for each study was assessed using validated tools according to the study design (online supplemental text 7) and classified as low, unclear or high. Data were organised by RMD and method used (online supplemental text 8), based on the classification proposed in the accompanying SLR.[6] Due to the broad heterogeneity, results were presented in the form of a narrative summary.

RESULTS

The search strategy yielded a total of 366 full-texts, of which 276 papers were related to methods to measure IFN-I pathway activation in RMDs in association with clinical outcomes. According to the different eligibility criteria depending on the research questions, overlapping sets of papers were included for each question (figure 1). Information about assay characteristics can be found in online supplemental text 8.

Research question 1: what is the evidence that interferon measurement is useful in the diagnosis of RMDs?

A total of 188 papers were reviewed. Since many papers included more than one assay or disease group, these resulted in 305 analyses related to the diagnostic role of IFN-I pathway activation, distributed as follows: SLE (n=139), rheumatoid arthritis (RA, n=34), primary Sjögren's syndrome (pSS, n=39), systemic sclerosis (SSc, n=39), dermatomyositis/polymyositis (DM/PM, n=32), antiphospholipid syndrome (APS, n=9), Behçet's disease (BD, n=6), vasculitis (n=1), ankylosing spondylitis

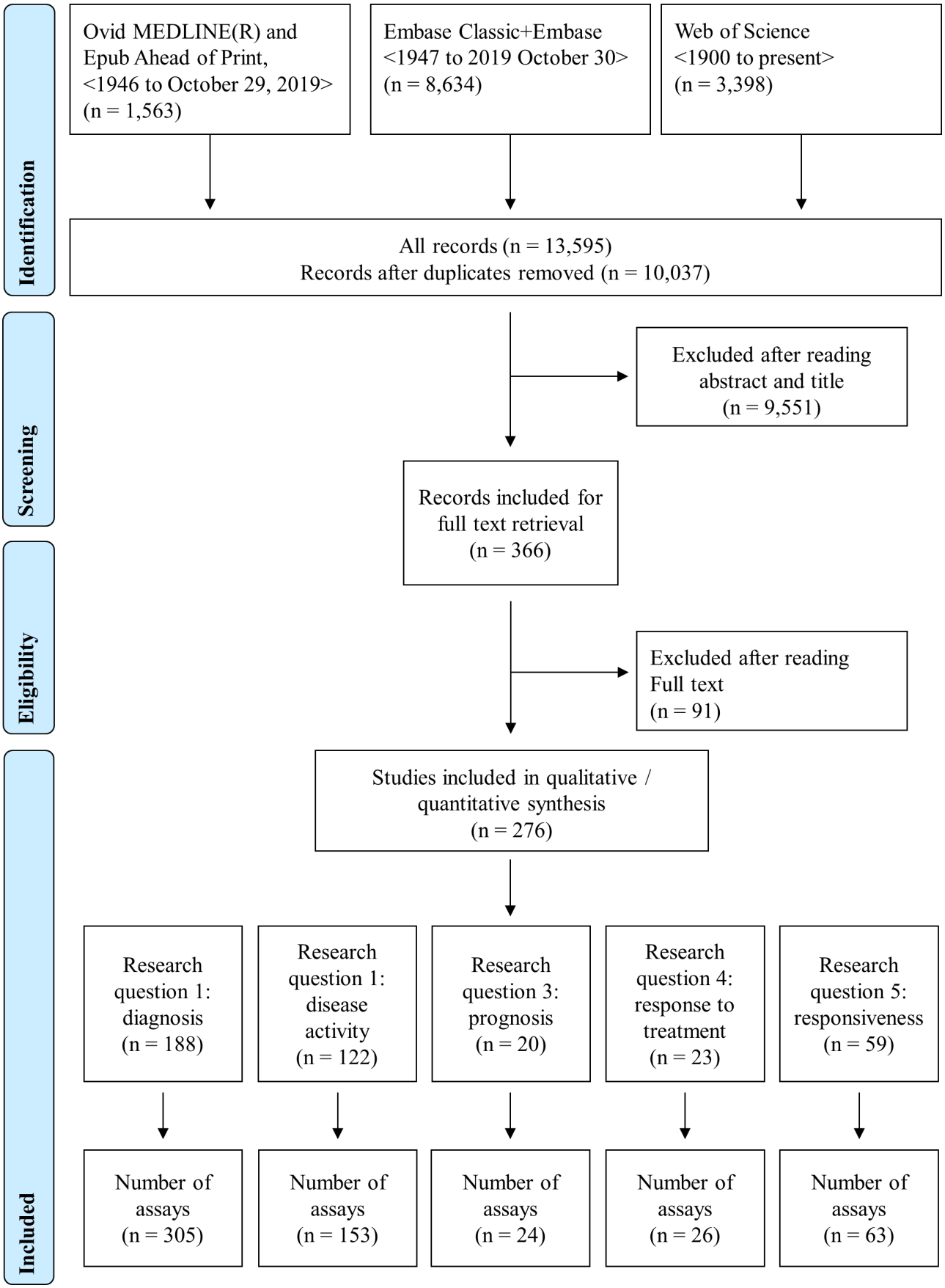

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. This flow chart shows the study selection and the search strategies. Since the different research questions proposed had different eligibility criteria, the number of excluded and included articles varies.

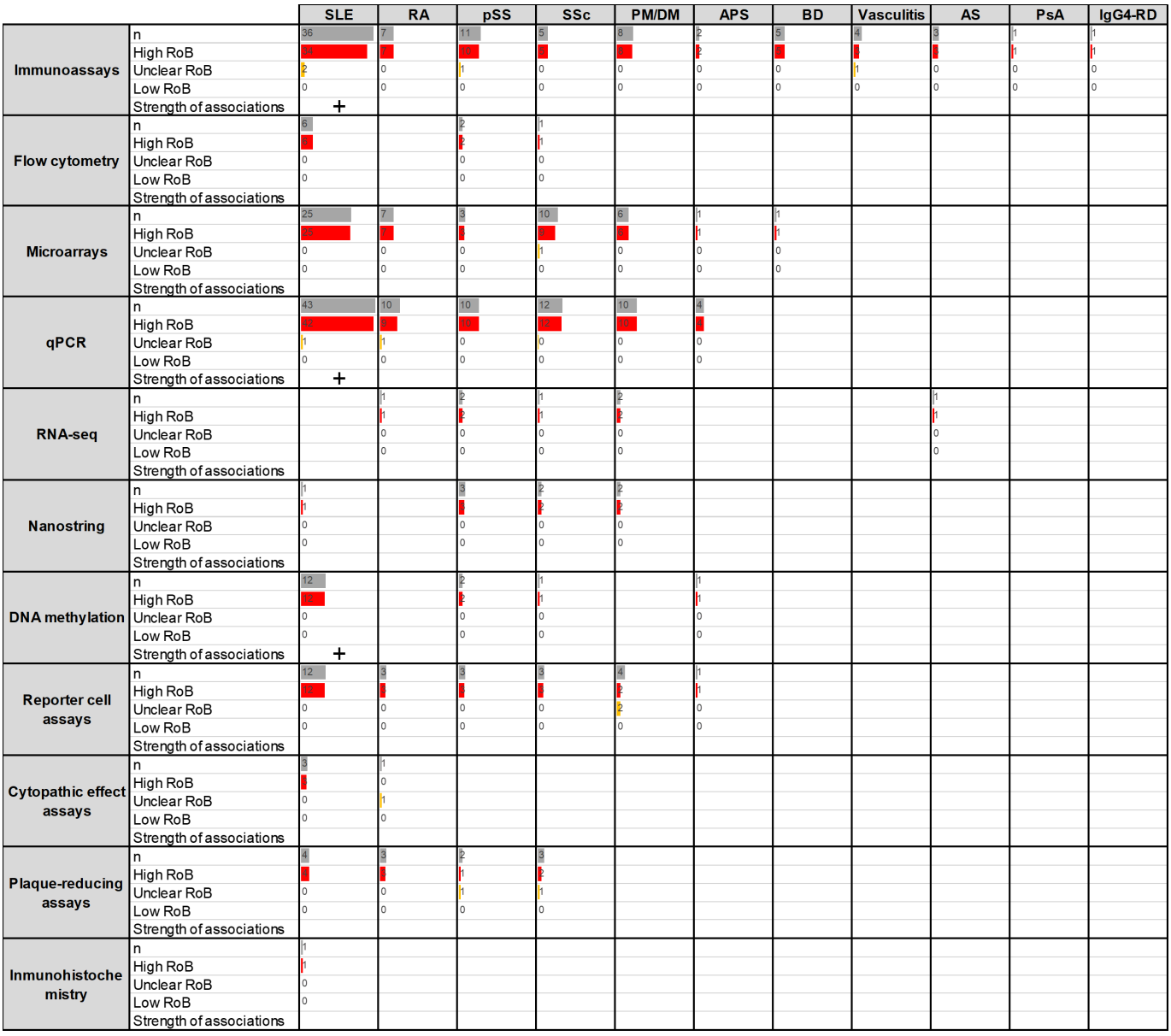

Figure 2 Summary of the studies reporting associations between IFN assays and diagnosis of RMDs (research question 1). Assays and RMDs are listed in rows and columns, respectively. The first number within each cell (n) represents the number of assays retrieved in the SLR for the corresponding technique and disease. The following numbers summarise the classification of these studies into RoB categories (high (red)/unclear (yellow)/low (green)). Bars are relative to the highest number of hits in the table. The strength of the associations (defined as the proportion of studies including diagnostic statistics) observed for each technique/disease combination is summarised as follows: '-': no associations, '+': <25%, '++': 25%–50%, '+++': 50%–75%, '++++': >75%. APS, antiphospholipid syndrome; AS, ankylosing spondylitis; BD, Behçet's disease; PM/DM, polymyositis/dermatomyositis; IFN, interferon; IgG4RD, IgG4-related disease; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; qPCR, quantitative PCR; RA, rheumatoid arthritis; RoB, risk of bias; RMD, rheumatic and musculoskeletal disease; RNA-seq, RNA sequencing; SLE, systemic lupus erythematosus; SLR, systematic literature review; SSc, systemic sclerosis.

(n=1), IgG4-related disease (IgG4RD, n=1) and psoriatic arthritis (PsA, n=1) (figure 2). The distribution of the different assays was not uniform, SLE, pSS and SSc being the conditions reporting a higher number of different techniques. The vast majority of the studies were classified as having a high risk of bias.

Systemic lupus erythematosus

From a total of 139 assays reported,[7–123] most of them used quantitative PCR (qPCR), immunoassays or microarrays. Most of the studies reported markedly increased IFN-I pathway activation in SLE compared with controls, but diagnostic statistics were scarcely reported and study designs did not usually recruit a prediagnosis population (online supplemental table 1). Studies on SLE using different methods consistently reported a substantial activation of the IFN-I pathway in patients, with percentages of patients classified as 'high' or 'positive' varying from 57% to 100%.

Rheumatoid arthritis

A total of 34 analyses were retrieved,[53 58 62 71 78 85 108 120 121 124–141] qPCR, immunoassays and microarrays being the most widely used. Studies using methylation or flow cytometry were not found. Again, studies did not recruit prediagnosis populations and little information was given regarding diagnostic statistics (online supplemental table 2). Overall, although the activation of the IFN-I pathway was confirmed by different techniques, the extent of the activation was relatively lower than in SLE (patients with RA classified as 'high' or 'positive' ranged from 13% to 45%). Within-group analyses revealed differences across disease stages (early vs established disease) as well as among subsets of interferon-stimulated genes (ISGs) in RA populations.[85 124 134 136 137]

Primary Sjögren's syndrome

In total, 39 analyses were found to evaluate differences between pSS and control populations.[68 84 89 97 103 110 116 120 121 127 142–157] Most of the analyses were performed by immunoassays or qPCR, and diagnostic statistics were only reported in methylation assays (online supplemental table 3). Overall, the papers identified confirmed an IFN-I pathway activation in pSS, but to a lower degree than in SLE patient populations (51% to 70% patients with pSS classified as 'high' or 'positive').

Systemic sclerosis

Thirty-nine analyses were observed to evaluate differences between SSc and control populations[42 48 53 58 84 89 97 116 120 121 158–172] (online supplemental table 4). The majority of them used qPCR or microarrays. Regarding immunoassay usage, most of them were directed against IFN-induced proteins, whereas the IFN-α protein was only assessed in one study. Different assays confirmed activation of the IFN-I pathway in SSc, but with important differences depending on clinical phenotypes (from 33% to 100%).[169]

Polymyositis/dermatomyositis

A total of 32 analyses were identified investigating the differences between patients with PM/DM and controls,[37 49 53 58 74 84 97 135 173–183] mostly using qPCR and immunoassays (although assays studying IFN-induced proteins were lacking) (online supplemental table 5). Despite the lower number of papers and assays, results in PM/DM were highly consistent and found a strong upregulation of the IFN-I pathway in PM/DM (especially in DM), to a similar degree to SLE.

Other RMDs

The literature search identified a lower number of papers focused on APS (9),[31 61 88 105 184–186] BD (6),[187–190] vasculitis (4),[190–192] ankylosing spondylitis (2),[189 193] PsA (1)[194] and IgG4-RD (1)[195] compared with control-matched populations. Immunoassays were the most used assays.

Summary

Although there were a considerable number of papers reporting differences in IFN-I pathway activation between different RMDs and control populations, most of the studies were correlative/associative studies; diagnostic statistics (area under the curve (AUC), specificity, sensitivity and predictive values) were only reported in a limited number of studies and were of high risk of bias from a diagnostic standpoint (mostly due to inappropriate study designs, knowledge of diagnosis status, interval between tests and lack of appropriate disease controls). None of the studies had an appropriate design to evaluate the diagnostic performance (pretest/post-test probability, likelihood ratios, etc). Therefore, the strength of association with clinical outcome was classified as low/very low. Prospective studies with preclinical autoimmunity or at-risk populations point to an association between IFN-I pathway activation and fulfilment of classification criteria in individuals reaching a diagnostic clinical outcome, thus strengthening the promising relevance of IFN-I pathway activation in relation to disease diagnosis and reinforcing the need for better study designs to address this question.

Stronger evidence was obtained for SLE (in terms of number of analyses reported and different techniques), where results were largely homogeneous. Of note, the IFN-I pathway association in this group was found to be consistently elevated and relatively higher than the rest of the RMDs studied. Results were also consistent in PM/DM. Less consistent results were observed for pSS, SSc and RA, in which differences by clinical features were reported. An additional point illustrated by this literature collectively is that since IFN-I pathway activation is seen in many RMDs, these assays may differentiate inflammatory RMDs from non-inflammatory conditions but may not be able to differentiate between multiple possible RMDs.

Research question 2: what is the evidence that interferon measurement reflects disease activity in RMDs?

A total of 122 papers were retrieved, which lead to 153 analyses related to the association between IFN-I pathway activation and disease activity distributed as follows: SLE (97), RA (15), pSS (12), SSc (9), DM/PM (17), vasculitis (2) and PsA (1) (figure 3). A significant proportion of studies were of high or unclear risk of bias (mostly due to the lack of confounding identification, adjustment and analysis). Again, the distribution of the different assays was not uniform, SLE being the condition reporting the highest number of different techniques and usage of several disease activity instruments.

Systemic lupus erythematosus

A total of 97 analyses of the association between disease activity and IFN-I pathway activation were identified,[7–9 12 13 15 17 19 20 22 24 25 27–29 31 32 36–42 45 47–51 53 59 64 66 67 69 72 75–78 81 82 85 86 90 92 93 98 99 101 106 107 115 116 118–120 122 123 130 196–213] mostly being immunoassays, qPCR and microarrays (online supplemental table 6). Overall, IFN-I pathway activation has

		SLE	RA	pSS	SSc	PM/DM	Vasculitis	PsA
Immunoassays	n	31	3	3	3	6	2	1
	High RoB	22	3	3	2	3	2	1
	Unclear RoB	4	0	0	1	0	0	0
	Low RoB	5	0	0	0	3	0	0
	Strength of associations	+++	++	+++	++++	+++	-	
Flow cytometry	n	5		2				
	High RoB	3		2				
	Unclear RoB	1		0				
	Low RoB	0		0				
	Strength of associations	++++		++++				
Microarrays	n	16	3	1	4	4		
	High RoB	14	1	1	3	2		
	Unclear RoB	1	2	0	1	0		
	Low RoB	1	0	0	0	2		
	Strength of associations	+++	-		++	++++		
qPCR	n	23	6	6	1	5		
	High RoB	16	2	0	0	0		
	Unclear RoB	3	4	2	1	2		
	Low RoB	4	0	4	0	3		
	Strength of associations	+++	++	++++		++++		
RNA-seq	n					1		
	High RoB					0		
	Unclear RoB					1		
	Low RoB					0		
	Strength of associations							
DNA methylation	n	4						
	High RoB	4						
	Unclear RoB	0						
	Low RoB	0						
	Strength of associations	++						
Reporter cell assays	n	5	1		1	2		
	High RoB	3	1		0	0		
	Unclear RoB	0	0		1	2		
	Low RoB	2	0		0	0		
	Strength of associations	+++				++		
Cytopathic effect assays	n	4	1					
	High RoB	4	1					
	Unclear RoB	0	0					
	Low RoB	0	0					
	Strength of associations	++++						
Plaque-reducing assays	n	3	1					
	High RoB	3	1					
	Unclear RoB	0	0					
	Low RoB	0	0					
	Strength of associations	++++						

Figure 3 Summary of the studies reporting associations between IFN assays and disease activity (research question 2). Assays and RMDs are listed in rows and columns, respectively. The first number within each cell (n) represents the number of assays retrieved in the SLR for the corresponding technique and disease. The following numbers summarise the classification of these studies into RoB categories (high (red)/unclear (yellow)/low (green)). Bars are relative to the highest number of hits in the table. The strength of the associations (defined as the proportion of studies reporting positive associations between disease activity measures and IFN assays) observed for each technique/disease combination is summarised as follows: '-': no associations, '+': <25%, '++': 25%–50%, '+++': 50%–75%, '++++': >75%. PM/DM, polymyositis/dermatomyositis; IFN, interferon; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; qPCR, quantitative PCR; RA, rheumatoid arthritis; RoB, risk of bias; RMD, rheumatic and musculoskeletal disease; RNA-seq, RNA sequencing; SLE, systemic lupus erythematosus; SLR, systematic literature review; SSc, systemic sclerosis.

been reported to reflect disease activity in patients with SLE, with results being highly consistent across populations and disease activity instruments, although the inclusion of serological biomarkers in the SLE Disease Activity Index (SLEDAI) is an additional bias for that instrument in the validation of other biomarkers. These studies were mainly cross-sectional. Regardless of the technique used, studies with a low risk of bias were consistent in reporting a positive association. A higher consistency was observed for flow cytometry, microarrays and functional

assays (cytopathic and plaque-reducing assays). When reported, correlation coefficients were homogeneous and moderate (0.3–0.6). Of note, the associations with disease activity may exhibit some differences depending on the organ affected,[47 75] thus suggesting that clinical domains should be taken into consideration when interpreting these associations and when comparing results from different populations or backgrounds.

Rheumatoid arthritis

From a total of 16 analyses retrieved,[53 71 85 124 125 129 131 136 137 140 141 214 215] most of the evidence came from qPCR and microarrays (online supplemental table 7). Most of the studies were of high or unclear risk of bias. Overall, there is some evidence that IFN-I pathway activation correlates to disease activity, but a low consistency across assays and important differences across disease stages were reported. When mentioned, coefficient correlations were often low and highly heterogeneous (ranging from −0.3 to 0.5).

Primary Sjögren's syndrome

A total of 12 analyses were found,[89 147 148 151–153 216 217] mostly using qPCR methods and immunoassays (online supplemental table 8). There is limited evidence that IFN-I pathway activation correlates with disease activity in patients with pSS, results being more consistent with flow cytometry and qPCR assays (especially those of low risk of bias, although most were classified as having high risk). As for the SLEDAI in SLE, the EULAR pSS Disease Activity Index instrument includes some immune biomarkers, which may introduce additional bias when validating other biomarkers.

Systemic sclerosis

The association between disease activity in SSc and IFN-I pathway activation was analysed in nine studies,[48 53 158 161 164 165 167] mostly from microarrays and immunoassays (online supplemental table 9) and of high/unclear risk of bias. There was limited evidence of a positive association, mostly with immunoassays, qPCR and functional assays, despite the low number of the latter.

Polymyositis/dermatomyositis

A total of 17 analyses were retrieved from the literature,[49 53 173 176–179 181 183 218 219] mostly reporting on immunoassays, qPCR and microarrays and showing a positive association with disease activity using different instruments (online supplemental table 10). Their results were very consistent across methods, especially in qPCR, microarrays and RNA sequencing, as well as in immunoassays to a lower extent. Correlation coefficients were homogeneous and moderate (from 0.4 to 0.8).

Other RMDs

Evidence was weaker in vasculitis (2)[190] and PsA (1),[194] all using immunoassays.

Summary

In general, there was evidence associating IFN-I pathway activation with disease activity in RMDs, most consistently in SLE and PM/DM, but also in RA and pSS to a lower extent. The number of different methods largely differed across RMDs. Most of the studies focused on qPCR, microarrays and immunoassays, with variable results across diseases. Despite being less reported, flow cytometry and functional assays were very likely to consistently exhibit positive associations with disease activity across RMDs. In addition to assay characteristics, variables such as the components of the disease activity instruments and clinical features (organ involvement, disease stage, etc) should be considered.

Overall, most of the studies were cross-sectional and associative and of unclear/high risk of bias. Despite the positive associations reported, the added clinical utility of measuring IFN-I pathway activation to monitor disease activity or whether they outperformed the current clinical instruments was not generally evaluated.

Research question 3: what is the evidence that interferon measurement is useful for the prognosis (natural history) of clinical status in RMDs?

A total of 20 papers were retrieved, resulting in 24 analyses related to the association between IFN-I pathway activation and disease prognosis as follows: SLE (20), RA (3) and SSc (1) (figure 4).

Systemic lupus erythematosus

A total of 20 analyses were retrieved relevant to the use of IFN-I pathway assays to predict flare development in patients with SLE,[36 45 54 75 81 83 92 97 104 107 198 199 202 204 220 221] mostly being immunoassays and qPCR (online supplemental table 11). Most of the analyses showed that IFN-I pathway activation could predict flare occurrence, defined by different clinical instruments and using different biosamples, along different follow-up periods (from 6 to 24 months), with a high consistency across methods. Studies with a low risk of bias (including appropriate confounding handling) were consistent in showing a positive predictive effect. There is some evidence that IFN-I pathway activation is a better predictor of flare (based on higher AUC, sensitivity or specificity values) than classical features (clinical or laboratory findings). However, other studies failed to confirm this. Of note, comparative analyses evaluating the added value of assays measuring IFN-I pathway activation over existing clinical instruments were scarcely reported. Therefore, the incremental value provided by analysis of the IFN-I pathway activation is uncertain.

Additionally, the use of IFN-I pathway assays in predicting progression from pre-clinical autoimmunity to clinical disease (SLE and/or others) has been also evaluated in a study with low risk of bias with positive results.[83] No associations were found in another study with a high risk of bias.[97] However, the type of assays, preclinical autoimmunity population studied and clinical outcomes limit comparative analyses.

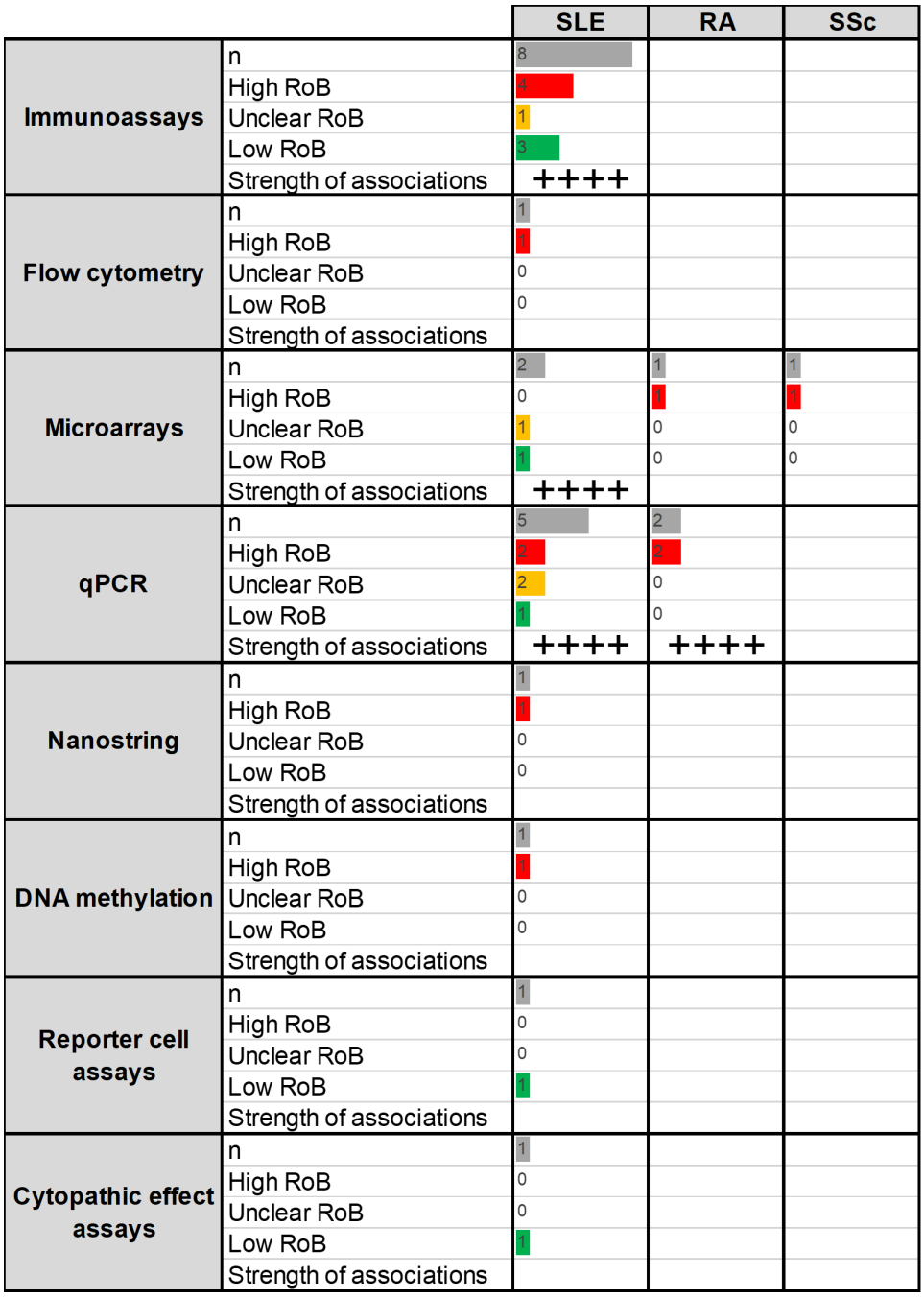

Figure 4 Summary of the studies reporting associations between IFN assays and disease prognosis (research question 3). Assays and RMDs are listed in rows and columns, respectively. The first number within each cell (n) represents the number of assays retrieved in the SLR for the corresponding technique and disease. The following numbers summarise the classification of these studies into RoB categories (high (red)/unclear (yellow)/low(green)). Bars are relative to the highest number of hits in the table. The strength of the associations (defined as the proportion of studies reporting IFN assays prospectively predicted disease outcomes) observed for each technique/disease combination is summarised as follows: '-': no associations, '+': <25%, '++': 25%–50%, '+++': 50%–75%, '++++': >75%. IFN, interferon; qPCR, quantitative PCR; RA, rheumatoid arthritis; RoB, risk of bias; RMD, rheumatic and musculoskeletal disease; SLE, systemic lupus erythematosus; SLR, systematic literature review; SSc, systemic sclerosis.

Rheumatoid arthritis

The use of IFN-I pathway assays to predict prognosis in RA was evaluated in three analyses,[137 222 223] focused on progression from arthralgia to clinical RA (2) and prediction of disease activity at follow-up (1) (online supplemental table 12). Microarray (1) and qPCR (1) studies supported an association between IFN-I pathway activation and progression to clinical RA. All studies were of high risk of bias.

Systemic sclerosis

One study was found to evaluate the association between IFN-I pathway activation and disease

progression in SSc,[163] thus reporting a negative correlation with increased forced vital capacity whereas no association was found with modified Rodnan skin score at 26 months (high risk of bias) (online supplemental table 13).

Summary

Evidence was supportive of the use of assays measuring IFN-I pathway activation in predicting disease prognosis, although depending on the prognostic outcome and disease context. Stronger evidence related to the prediction of flares in SLE populations, mostly by immunoassays and qPCR methods. A single higher-quality study supported the prediction of progression to clinical disease in antinuclear antibody–positive individuals. Better clinical characterisation of these populations, confounder identification and handling as well as clinical validation remain suboptimal for other questions and contexts.

Research question 4: what is the evidence that interferon measurement is useful for the prognosis of the response to treatment in RMDs?

A total of 23 papers were retrieved, leading to 26 analyses related to the association between IFN-I pathway activation and response to treatment distributed as follows: SLE (5), RA (15), PM/DM (4) and pSS (2) (figure 5).

Systemic lupus erythematosus

A total of five analyses evaluated the association between IFN-I pathway activation, mostly using qPCR methods, and response to treatment with four different agents, including therapies targeting the IFN-I pathway[54 224–227] (online supplemental table 14). One study with tabalumab (anti-B-cell-activating factor) using microarrays failed to show any association.[54] Among studies with antibodies against IFN-α protein, one study (using sifalimumab) showed no association,[227] whereas another study (using rontalizumab) concluded that IFN-I pathway activation could predict clinical response. In this study, better

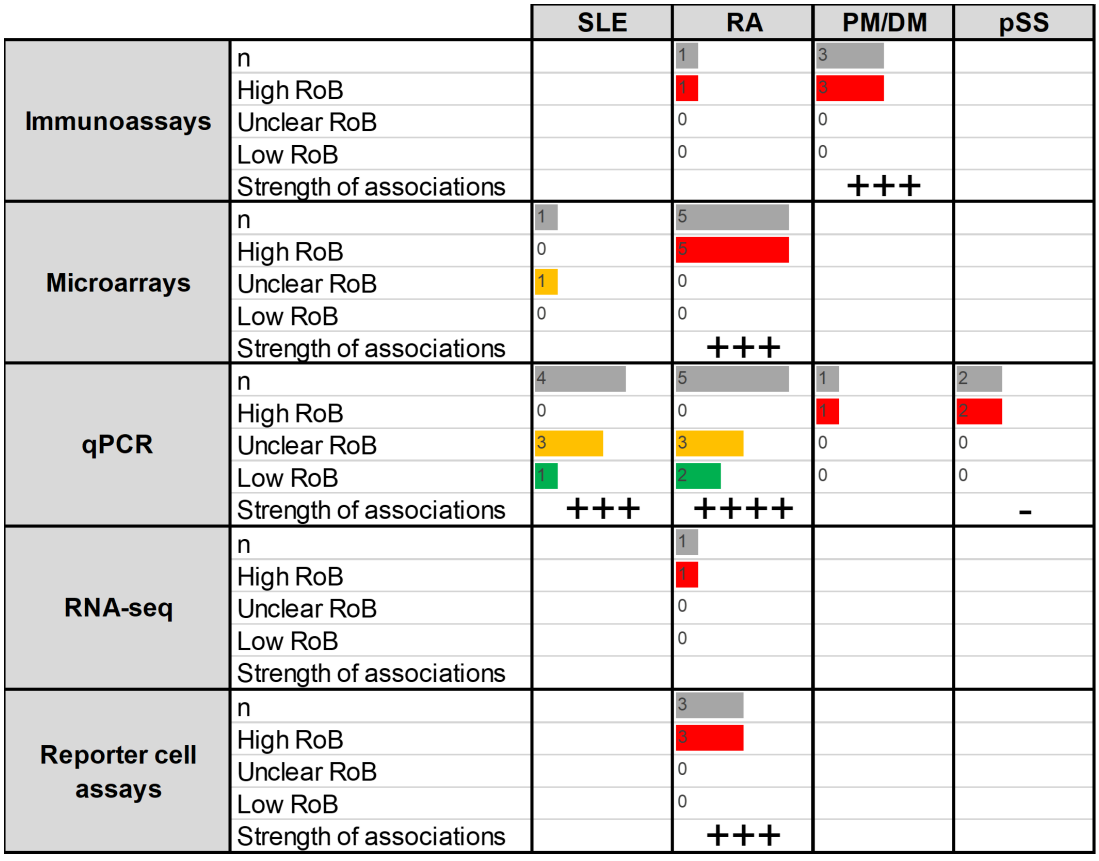

Figure 5 Summary of the studies reporting associations between IFN assays and response to treatment in RMDs (research question 4). Assays and RMDs are listed in rows and columns, respectively. The first number within each cell (n) represents the number of assays retrieved in the SLR for the corresponding technique and disease. The following numbers summarise the classification of these studies into RoB categories (high (red)/unclear (yellow)/low (green)). Bars are relative to the highest number of hits in the table. The strength of the associations (defined as the proportion of studies reporting IFN assays predicted response to treatment) observed for each technique/disease combination is summarised as follows: '-': no associations, '+': <25%, '++': 25%–50%, '+++': 50%–75%, '++++': >75%. PM/DM, polymyositis/dermatomyositis; IFN, interferon; pSS, primary Sjögren's syndrome; qPCR, quantitative PCR; RA, rheumatoid arthritis; RoB, risk of bias; RMD, rheumatic and musculoskeletal disease; RNA-seq, RNA sequencing; SLE, systemic lupus erythematosus; SLR, systematic literature review.

response to IFN-I blockade was observed in patients with low IFN-I pathway activation.[225] On the contrary, studies with anifrolumab (2)—all randomised controlled trial (RCT) with low/unclear risk of bias, using different clinical response criteria—reported that increased IFN-I pathway activation was predictive of better clinical response, in contrast to results for rontalizumab.[224 226]

Rheumatoid arthritis

The use of IFN-I pathway activation to predict treatment outcomes was evaluated in 15 analyses,[125 131 136–139 214 215 222 228–232] mostly by microarrays and qPCR methods (online supplemental table 15). IFN-I pathway activation was found to predict clinical response to anti-tumour necrosis factor (anti-TNF)[125 131 136 138 139 214 232] (unclear/high risk of bias) and the anti-CD20 monoclonal antibody rituximab[215 228 230 231] (low/unclear risk of bias) using different assays. However, the direction of the association between IFN-I pathway activation and clinical response to anti-TNF treatment was different in studies using different assays, biosamples and sample timings. Functional assays highlighted the need of combined qualitative (ie, the relative contribution of the actual IFN proteins underlying IFN-I pathway activation) and quantitative approaches (ie, the absolute level of IFN-I pathway activation).[232] There was also some consistent but limited evidence on conventional synthetic disease modifying antirheumatic drug (csDMARD),[136 137] and rather limited with tocilizumab (anti-interleukin 6 monoclonal antibody).[229]

Polymyositis/dermatomyositis

Four analyses addressing the use of IFN pathway activation and clinical response in PM/DM were retrieved[233 234] (online supplemental table 16). The association with clinical response to combined immunosuppressive agents (3)[233] was not consistent among assays, with significant associations being observed in qPCR and immunoassays (only with some outcomes). The results with rituximab (1)[234] were significant although variable across clinical outcomes and antibody status.

Primary Sjögren's syndrome

The use of IFN-I pathway assays to predict treatment outcomes in pSS was evaluated in two studies[152 235] (online supplemental table 17). No significant associations were found.

Summary

There was consistent evidence that measuring the IFN-I pathway activation by gene assays predicted better response to IFN-I targeting therapies in SLE across RCTs. Other than this, while there were a number of relatively high-quality studies reporting an association between IFN-I pathway activation assays and response to therapy in RMDs, especially in SLE, some of the results appeared contradictory. A potential issue here relates to the properties of the IFN-I pathway biomarkers described above. These biomarkers associate with baseline disease activity, clinical features and serological markers, which may themselves predict response to both standard of care and investigational targeted therapy. To what extent IFN-I pathway activation outperforms these variables and existing instruments is yet to be elucidated.

Research question 5: what is the evidence that interferon measurement is responsive to changes with changing disease status or treatment?

A total of 59 papers were retrieved, leading to 63 analyses related to the association between IFN-I pathway activation and assay responsiveness (change over time) as follows: SLE (31), RA (11), SSc (3), pSS (6) and PM/DM (10) (figure 6).

Systemic lupus erythematosus

Among 32 analyses retrieved, 18 studies analysed the changes in IFN-I pathway activation on initiation of novel treatment or modification of treatment dosages,[15 40 54 59 64 78 79 90 94 130 208 236–239] whereas 14 analysed fluctuations in the absence of group-level changes in treatments[9 47 72 82 108 110 117 123 196 204 206 213 240–242] (online supplemental table 18). The use of novel treatment regimens was associated with decreases in IFN-I pathway activation, mostly with drugs targeting this pathway,[59 64 90 94 130 238 239] but also with high doses of glucocorticoids (oral or intravenous).[40 208] Studies with a low risk of bias were consistent in this regard. These changes were observed in the short (few days) and the long term (until 6 months) and were consistent across methods. Biological drugs not targeting the IFN-I pathway (omalizumab: anti-IgE,[237] tabalumab: anti-B-cell activating factor[54]) and other agents (hydroxychloroquine,[15] vitamin D[236]) did not modulate IFN-I pathway activation. In most of the studies with no group-level changes in treatment, no fluctuations (5) or uncertain patterns (2) were observed in IFN-I measurements. Of note, microarrays revealed heterogeneity among expression modules. For example, module 5.12 was more responsive to change in clinical status than module 1.2, with the latter including the ISGs most commonly measured in other qPCR studies.[43 47] Studies finding fluctuations in IFN-I pathway activation (6) reported parallel changes in disease trajectories (disease exacerbation, flares, remission).

Rheumatoid arthritis

From 18 analyses identified in the literature[85 124 136 137 214 222 228 232 243 244] almost all came from studies analysing changes in treatments (online supplemental table 19). Studies in patients initiating anti-TNF treatment (5) did not reveal changes in IFN-I pathway activation,[85 136 214 222] except in a study using a functional assay.[232] The retrieved studies used different methods and a similar timeframe (from 1 to 3 months). Evidence from studies with other agents (anakinra (1),[243] combined csDMARDs (1)[137] and rituximab (1)[228]) was more limited but suggested

		SLE	RA	SSc	pSS	PM/DM	APS	BD	PsA
Immunoassays	n	6	1	2	2	3	2	1	1
	High RoB	1	0	0	2	0	2	1	1
	Unclear RoB	3	1	2	0	2	0	0	0
	Low RoB	2	0	0	0	1	0	0	0
	Responsiveness	TC ++ TU ++		TC ++++	TC ++++	TC +++			
Flow cytometry	n	2			1				
	High RoB	1			0				
	Unclear RoB	0			1				
	Low RoB	1			0				
	Responsiveness	TC ++++							
Microarrays	n	8	2	1		1			
	High RoB	1	0	0		0			
	Unclear RoB	4	1	1		1			
	Low RoB	3	1	0		0			
	Responsiveness	TC ++++ TU ++	TC ++						
qPCR	n	11	7		2	5			
	High RoB	4	0		1	2			
	Unclear RoB	5	2		1	1			
	Low RoB	2	5		0	2			
	Responsiveness	TC ++++ TU ++	TC +			TC ++++ TU +++			
Reporter cell assays	n	2	1		1	1			
	High RoB	2	0		0	0			
	Unclear RoB	0	1		1	0			
	Low RoB	0	0		0	1			
	Responsiveness	TU ++++							
Cytopathic effect assays	n	2							
	High RoB	2							
	Unclear RoB	0							
	Low RoB	0							
	Responsiveness	TU -							
Plaque-reducing assays	n	1							
	High RoB	1							
	Unclear RoB	0							
	Low RoB	0							
	Responsiveness								

Figure 6 Summary of the studies reporting responsiveness to change of IFN assays in RMDs (research question 5). Assays and RMDs are listed in rows and columns, respectively. The first number within each cell (n) represents the number of assays retrieved in the SLR for the corresponding technique and disease. The following numbers summarise the classification of these studies into RoB categories (high (red)/unclear (yellow)/low (green)). Bars are relative to the highest number of hits in the table. The strength of the associations (defined as the proportion of (studies reporting significant changes) observed for each technique/disease combination in patients with treatment changes (TC) or treatment unchanged (TU, usual/standard care) observed for each technique/disease combination is summarised as follows: '-': no associations, '+': <25%, '++': 25%–50%, '+++': 50%–75%, '++++': >75%.APS, antiphospholipid syndrome; BD, Behçet's disease; PM/DM, polymyositis/dermatomyositis; IFN, interferon; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; qPCR, quantitative PCR; RA, rheumatoid arthritis; RoB, risk of bias; RMD, rheumatic and musculoskeletal disease; SLE, systemic lupus erythematosus; SLR, systematic literature review; SSc, systemic sclerosis.

potential changes (in different directions) in IFN-I pathway activation on initiation of treatment.

Systemic sclerosis

Among three analyses retrieved from the literature, two came from studies with changes in treatment regimens to immunosuppression with cyclophosphamide and revealed suppression of the IFN-I pathway activation using different methods (immunoassays and microarrays)[163] (online supplemental table 20). Studies with no group-level changes in treatment[161] found unaltered IFN-I pathway activation in long follow-ups (>2 years).

Primary Sjögren's syndrome

From six analyses identified in the literature,[142 148 152 153 157] five of them revealed suppression of the IFN-I pathway activation in patients starting new treatments, mainly rituximab (2)[142] and HCQ (2)[148 152] (online supplemental table 21). Only one analysis was

retrieved with no changes in treatment and revealed unaltered IFN-I pathway activation.

Polymyositis/dermatomyositis

Among 10 analyses retrieved from the literature, 7 analysed the effect of novel treatments and most of them revealed changes in IFN-I pathway activation in relation to clinical improvement along different time points[178 233 234 245–247] (online supplemental table 22). Results were more consistent with immunosuppressive-combined regimens (3)[178 233] and not consistent with rituximab (2),[234 245] whereas other drugs (sifalimumab and the anti-TNF infliximab) were less studied. Fluctuations in IFN-I pathway activation were also found in studies with no changes in treatments (3),[176 177 219] but changes in disease activity were reported in parallel in all cases. Patients with no or little changes in disease activity were found not to exhibit fluctuations in IFN-I pathway activation.[176 177]

Other RMDs

Analyses of changes in IFN pathway activation were also identified in vasculitis (1)[190] and PsA (1)[194] populations, with very low sample sizes in both cases (n<10).

Summary

IFN-I pathway activation seemed to be stable over time at the group level across different RMDs and different assays in the absence of systematic treatment changes or disease activity fluctuations (exacerbation or remission). However, in studies in which groups of patients started the same treatment, there was evidence that certain treatments can modulate IFN-I pathway activation, especially drugs targeting the IFN-I pathway and high-dose glucocorticoids; the effect of other agents seems to be weaker and differed across RMDs. Of note, not all ISGs or gene modules exhibited the same assay responsiveness.

DISCUSSION

Despite the pivotal role of IFN-I in the pathogenesis of RMDs, the numerous assays for this pathway have so far not successfully translated into clinical practice. The aim of this SLR was to provide a comprehensive review of the existing evidence to understand causes, identify gaps and provide solid foundations to enable future clinical and research applications of IFN-I assays. This is the first study where the evidence underlying the analysis of IFN-I pathway activation in rheumatology is investigated in a systematic manner. A key strength of this review is that it provides an overall picture of findings, since a large number of RMDs were included and the clinical questions formulated covered the entire disease process.

Evidence has been encouraging for the potential role of IFN-I pathway activation as a biomarker in several RMDs with different clinical applications and outcomes. However, despite extensive research over the last decades, our SLR revealed (1) an enormous diversity of assays, (2) a high methodological heterogeneity, also related to reporting and analysis and (3) a number of important flaws. Several issues were detected in study design, clinical validation, outcome definition and assessment, gold standard definition, as well as in the analysis and reporting of the results. These issues prevented the possibility of performing pooled analyses to generate robust, first-level clinical evidence. Taken together, these points may account for the lack of transition of IFN-I assays into routine care and emphasise the need for harmonisation of the clinical and experimental requirements along the whole process (from sample choice and collection to results reporting). Although our SLR was focused on RMDs, the observed methodological concerns are not rheumatology-specific, and due to the involvement of IFN-I pathway activation in other areas,[248–250] our findings might be generalisable to other clinical fields.

An important message from our SLR is that although there was a certain degree of consistency among IFN-I pathway assays for a given research/clinical question, there was not a single, universal assay that can satisfy all the needs. This may be explained, at least in part, by the fact that by measuring different components of the IFN-I pathway, they likely provide different information. From a biological standpoint, there is a huge difference in measuring the production of IFN proteins (which belong to different subtypes in different proportions depending on the stimulus and require highly sensitive and reliable assays) compared with the cellular response(s) to IFNs (which can be analysed at functional or genetic levels by several read-outs and may differ in their specificity to the IFN proteins). These differences may provide a different degree of added value for a clinical question. In this sense, there is a need for more comparative studies using different assays, both in terms of head-to-head analyses to allow direct and indirect comparisons across assays, but also in terms of simultaneous assessments in several RMDs to evaluate if the clinical added value is similar across the RMD spectrum or if, on the contrary, it needs to be regarded as disease-specific. Furthermore, whether this added clinical value may be seen by using combinations of different assays or combinations with other signatures and biomarkers remains to be explored.[43 251]

Another remarkable finding from this review was that the level of evidence about the value of IFN-I assays across RMDs and clinical outcomes within a single RMD was largely skewed. This may reflect that the use of IFN-I assays has been proposed to resolve disease-specific unmet clinical needs, so it may be difficult to compare its overall value in different disease scenarios. Moreover, differences in added value may be also obscured by the use of different treatment modalities across different RMDs, hence underscoring the need of evaluating untreated populations and/or appropriate analysis adjustments by treatment.[252]

From a clinical perspective, an important flaw detected in the existing literature was the noticeable lack of the well-designed diagnostic studies, despite yielding the highest number of hits. Regarding the remaining clinical

endpoints, evidence was consistent about the use of IFN-I assays to predict disease prognosis in patients with SLE (flare occurrence), as well as to monitor disease activity (although with less evidence about its added value and potential confounding due to serological markers in composite indices). In RA, heterogeneous associations were linked, at least in part, to the disease stage, so the choice and target(s) of the assay may need to be adapted along the disease course. An equivalent picture was observed in SLE populations depending on organ involvement. It must be noted that IFN-I assays have been also linked to several clinical features and patient-reported outcomes. Recent evidence suggests that some assays fail to exhibit an association with fatigue in SLE and pSS,[96 253 254] whereas some immunoassays[255 256] and gene expression assays[257–259] showed conflicting results, hence strengthening the need for careful selection of assays and target(s) depending on the clinical question.

Regarding the prediction of response to treatment, evidence was stronger for SLE in general and consistent for drugs targeting the IFN-I pathway. Following the analysis of this SLR, an additional major study with a pooled population from two phase III RCTs with anifrolumab demonstrated a better response in patients with a high IFN-I pathway activation across different clinical endpoints.[260] One further RCT of a non-IFN-targeted therapy (iberdomide) also showed positive results for the prediction of response using a similar gene assay.[261] Therefore, the latest evidence reassured the findings of our SLR. Furthermore, IFN-I pathway activation might be related to the progression from preclinical autoimmunity to clinical disease, with limited evidence coming from SLE-related and RA-related studies. However, it is important to note that the incremental, added value provided by IFN-I assays was difficult to evaluate due to the lack of established instruments which to be validated. Finally, the analyses of the responsiveness of IFN-I assays yielded a relatively uniform message across RMDs. IFN-I pathway activation measurements seemed to be relatively stable over time in the absence of systematic changes in treatments or disease status.

This review has some limitations. Although we used a sensitive approach to identify all the available studies, a potential effect of publication bias cannot be excluded, which may lead to an overestimation of 'positive' results (more likely to be published). Moreover, the heterogeneity observed prevented the use of meta-analyses or pooled analyses. Moreover, RMDs were grouped according to classification criteria to allow a global comparison across conditions. However, whether differences by disease stage, clinical features (including patient-reported outcomes), and treatment modalities should be considered to evaluate the clinical value of IFN-I pathway activation in disease subsets has not been addressed in the present SLR. Regarding bias assessments, it is important to note that for some research questions, the results of the small number of higher-quality studies are not negated by the less certain or contradictory findings of more numerous low-quality studies.

In conclusion, evidence is supportive of the clinical value of IFN-I pathway activation in RMDs, although the results herein reported revealed a high methodological heterogeneity, risk of bias and important flaws in IFN-I research in this field. In addition to putting figures into these aspects, this SLR urges a need for harmonisation and implementation of a minimum number of elements around these flaws when reporting and performing future research. This SLR informs the ongoing EULAR points to consider for the measurement, reporting and application of IFN-I pathway activation assays in clinical and research practice.

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