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## Review article

# Systematic review of infliximab-induced autoantibodies and systemic lupus erythematosus<sup>☆</sup>

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## ABSTRACT

The present systematic review aims to discuss infliximab-induced autoantibodies and subsequent onset of systemic lupus erythematosus (SLE) through the analyses of primary reports measuring autoantibodies both before and after the administration of infliximab for the treatment of several diseases – e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease. Our literature search was performed in nine databases – PubMed, Science Direct, Scopus, Web of Knowledge, Scirus, Cochrane, EMBASE, Scielo and LILACS, and the search query retrieved 998 primary reports, from which 24 articles were selected and further narrowed down to 14, based on our inclusion criteria. Two independent reviewers performed the article selection and a third reviewer solved discrepancies. Our inclusion criteria comprised primary reports of phase IV clinical trials with duration of at least three months. In total, 760 patients were evaluated and the most prevalent assays performed in the studies were anti-nuclear antibodies (ANA), anti-double stranded DNA antibodies (anti-dsDNA), and antibodies to saline-extracted antigens (ENA panel). Of all patients evaluated, 10 (1.3%) showed clinical signs and laboratorial evidence of infliximab-induced SLE.

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## Revisão sistemática da indução de autoanticorpos e lúpus eritematoso pelo infliximabe

### RESUMO

Nesta revisão sistemática abordamos a indução de autoanticorpos e lúpus eritematoso pelo infliximabe, analisando estudos que dosaram vários autoanticorpos antes e após o uso do infliximabe em diversas doenças (artrite reumatoide, espondilite anquilosante, artrite psoriásica e doença de Crohn). Nossa busca foi realizada em nove bases de dados (PubMed, ScienceDirect, Scopus, Web of Knowledge, Scirus, Cochrane, EMBASE, Scielo e LILACS).

### Palavras-chave:

Infliximabe

Terapia biológica

Autoanticorpos

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Foram encontradas 998 referências; 24 artigos foram separados na íntegra, dos quais 10 foram excluídos por não entrarem em nossos critérios de seleção. A escolha dos artigos foi realizada por dois revisores, e as divergências foram resolvidas por um terceiro revisor. Incluímos estudos de fase IV, com no mínimo três meses de duração. No total foram estudados 760 pacientes; o fator antinuclear, o anticorpo anti-DNA de dupla hélice e os antígenos extraídos pela salina foram os mais verificados. De todos os pacientes, apenas 10 (1,3%) apresentaram manifestações clínico-laboratoriais de lúpus induzido por infliximabe.

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## Introduction

The advent of biological therapy has changed the treatment profile of autoimmune diseases. However, despite more than a decade using anti-tumor necrosis factor (anti-TNF) agents, many questions still remain. One of the most important is the association between autoantibody induction and certain diseases such as drug-induced lupus (DIL). The present study is a systematic review on the role of infliximab as an autoantibody inducer, discussing what has been published in this regard.

Regarding immune responses after antigen stimulation, according to the local cytokine environment, T CD4 + naïve proliferate and differentiate into different effector subtypes with their own characteristics (Th1, Th2, Th3, Treg, Th17) determined by the profile of the produced cytokines and the functional properties. Thus, Th1 or Th2 profile cytokines guide the development of their respective pathway, inhibiting the opposite pattern expression.

Thus, once the immune response to the Th1 pattern is polarized, the Th2 pathway will be inhibited, and vice versa.<sup>1</sup> As the anti-TNF agents inhibit Th1 response, there could be an increase in the occurrence of Th2 profile autoimmune phenomena, such as systemic lupus erythematosus (SLE). However, the occurrence of SLE has been only occasionally reported, although the production of antinuclear factors and autoantibodies is much more frequent.<sup>2-4</sup> It is noteworthy how difficult it is to prove DIL caused by a particular medication, as symptoms must improve with the drug withdrawal (days to weeks after discontinuation) and reappear or reaggravate the disease by restarting it. However, it is difficult to do so in clinical practice. In addition, the medication should have been employed for at least a month, but perhaps these data do not apply to biological agents.<sup>5</sup>

When one talks about DIL, one must remember that the symptoms are somewhat different from those seen in SLE, with arthralgia, myalgia, fever, malaise and serositis being more common, whereas kidney lesions and neurological disorders are uncommon. The classic skin manifestations of SLE such as malar rash and discoid lesions are uncommon in DIL, with nonspecific lesions (erythema nodosum and purpura) being more frequent in this case. However, cases of lupus induced by anti-TNF, especially infliximab, can show classic lesions such as malar rash and discoid lupus.<sup>6</sup> From the laboratory point of view, reactive antinuclear antibodies (ANA) are commonly found, as well as leukopenia, thrombocytopenia, anemia and anti-histone antibodies. The latter, in fact, is a nonspecific one,

as it can also be observed in SLE.<sup>7</sup> Laboratory findings may take several months to disappear after drug withdrawal.<sup>8</sup>

Although anti-TNF therapy favors the appearance of autoantibodies, clinical autoimmune complications are rare.<sup>9</sup> In relation to the production of autoantibodies by anti-TNF agents, some mechanisms have been proposed: a) as the anti-TNF reduces acute phase proteins and phagocytosis of apoptotic cell debris, the persistence of nuclear debris would be immunogenic, which would lead to autoantibody synthesis induction;<sup>10</sup> b) Anti-TNF could induce the apoptosis of TNF-producing cell and inhibit clearance of these apoptotic cell debris, which in turn would be immunogenic and induce the synthesis of autoantibodies.<sup>11</sup> In this review we chose to use only infliximab, as considering that this drug is a chimeric anti-TNF agent, it contains an immunogenic murine portion, whereas the other biological agents of this class are human, thus having a lower chance of inducing autoimmune phenomena.

## Methods

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.<sup>12</sup>

### Databases and search strategies

The search was carried out in nine databases (PubMed, ScienceDirect, Scopus, Web of Knowledge, Scirus, Cochrane, EMBASE, LILACS and SciELO, including the so-called gray literature (Scirus). There were no language restrictions. All articles found until January 2012 were evaluated. A librarian with experience in systematic reviews helped to prepare the following search strategy based on the *PubMed* database: #2 Search infliximab; #4 Search (“autoantibodies”[MeSH Terms]) OR “autoimmune diseases”[MeSH Terms]) OR “autoimmunity”[MeSH Terms]#8:21:05359160; #7 Search (“arthritis, psoriatic/drug therapy”[MeSH Terms]) OR “psoriasis/drug therapy”[MeSH Terms]) OR “spondylitis, ankylosing/drug therapy”[MeSH Terms]) OR “Crohn’s disease/drug therapy”[MeSH Terms]) OR “proctocolitis/drug therapy”[MeSH Terms]) AND “arthritis, rheumatoid/drug therapy”[MeSH Terms]#8:24:33805. Equivalent strategies were used in other databases.

The electronic search database was created with the help of the Web endnote software. Duplicate citations were excluded. Relevant titles and abstracts were selected by two reviewers (JLP Vaz, Pereira AC) and disagreements were resolved by consensus or by a third reviewer (Andrade CAF), when necessary.

### Selection criteria and data extraction

Only articles related to clinical trials and cohort studies that included the measurement of autoantibodies before and after the use of infliximab were selected; case reports and review articles were excluded. Only studies with a minimum duration of three months, in which infliximab was the first biological agent used and patients were adult individuals aged 18 and older were accepted. Articles that included patients with more than one autoimmune disease were excluded. Among the diseases, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), psoriasis, Crohn's disease and ulcerative colitis were selected. These diseases were chosen because infliximab can be used in any of these diseases by adult patients.

We chose to compare autoantibody variability only (before and after use of infliximab), regardless of the titration. Studies that included the following antibodies/methods were accepted: antinuclear antibodies (ANA) by indirect immunofluorescence on HEp-2 cells (regardless of the cutoff); anticardiolipin (aCL) by ELISA; anti-double-stranded (anti-dsDNA) or anti-native DNA (anti-nDNA) by indirect immunofluorescence using as substrate *Crithidia luciliae* and other autoantibodies [saline-extracted antigens (total anti-ENA), anti-histone, anti-single stranded DNA (anti-ssDNA), anti-Ro, anti-La, anti-Sm, anti-ribonucleoprotein (anti-RNP), anti-topoisomerase (anti-Scl70), anti-mitochondrial, anti-thyroid, anti-neutrophil cytoplasmic antibody (ANCA), anti-nucleosome, anti-flaggrin, anti-liver-kidney microsome antibodies (anti-LKM) and anti-adrenal antibody. Articles that assessed only rheumatoid factor and anti-citrullinated protein antibodies (ACPA) were excluded from this review.

### Results

A total of 998 articles were found, of which 79 abstracts were initially selected and subsequently, 24 full articles. Of the 998 articles found, 919 abstracts were excluded because although they were retrieved by the electronic search, they did not meet

the inclusion criteria (Fig. 1). In spite of the thorough search of cross-references in the selected articles, no additional article was found. A total of 760 patients were studied and articles from the following countries were assessed: Belgium, Canada, France, Israel, Italy and Sweden (Table 1).

ANA was evaluated in almost all studies selected in this systematic review (Table 1). The total number of patients with ANA assessment was 695, of which 199 (28.6%) had reactive ANA before infliximab use. After the medication use (on average after six months, as only one study had a three-month duration), the total number of patients with reactive ANA was 469 (67.5%), i.e., there was a variation of 38.9% of reactive patients before and after infliximab use (Table 2).

Regarding the anti-dsDNA, two studies did not evaluate it separately (Table 1). Thus, the total number of evaluated cases was 669. In the beginning, before infliximab use, only eight cases (1.2%) were reactive, whereas after treatment, 117 (17.5%) patients were reactive, with a variation of 16.2% (Table 2).

As for anti-ssDNA, only two studies assessed this antibody. Vermeire et al.,<sup>26</sup> in 2003, found this antibody in approximately 14% (17 of a total of 125) patients after infliximab use for 12 months. Comby et al.,<sup>16</sup> in 2006, showed that after six months of infliximab use there was a 12% increase in the number of patients with high titers of anti-ssDNA.

The studies that evaluated the total anti-ENA (Table 1) showed no case before or after treatment (Table 2). All four studies (Table 1) that analyzed saline-extractable antigens (anti-ENA) separately found a total of 208 cases, with anti-Ro varying from four (1.9%) to five (2.4%) cases before and after infliximab, respectively. As for anti-RNP, there was only one case (0.6%) before and 12 (7.3%) cases after infliximab use, with a 6.7% (n = 165) variation. Before medication there were two patients (1.2%) with reactive anti-La and after medication that number increased to only three cases (1.8%), with a 0.6% variation (n = 165). There was only one case (0.7%) with reactive anti-Sm (n = 139), with no alterations after treatment.

Six studies (Table 1) evaluated aCL in a total of 222 patients. Before treatment, 21 (9.5%) cases were reactive, but at the end of treatment 49 (22%) of cases were reactive, with a variation of 12.5% (Table 2). There were no cases of anti-Beta 2 GP1 be-

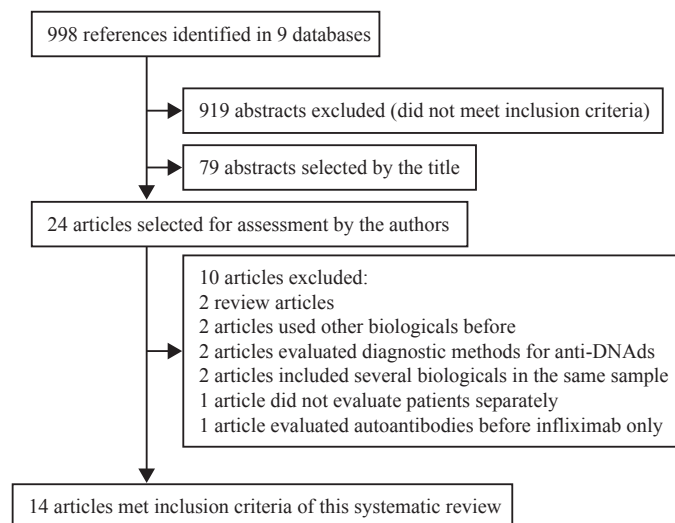


Figure 1 – Flowchart showing the study selection process.

**Table 1 – Epidemiologic, disease and autoantibody data of the analyzed studies.**

Author/ year	Country	N	F/M	Age mean (years)	Diseases	Time of disease (years)	Study duration (months)	Autoantibodies
Allanore <sup>13</sup> 2004	France	59	54/05	54 (41-68)	RA	14 (05-23)	7.5	ANA, anti-dsDNA, anti-histone, total anti-ENA
Bobbio-Palavicini <sup>14</sup> 2004	Italy	30	24/06	57 (48-66)	RA	9 (1-17)	18	ANA, anti-dsDNA, aCL
Caramaschi <sup>15</sup> 2006	Italy	43	37/06	52 (40-64)	RA	14 (5-23)	12	ANA, anti-dsDNA, ANCA, anti-mitochondrial, anti-thyroid, anti-Ro
Comby <sup>16</sup> 2006	France	58	44/14	54 (42-66)	RA	13 (04-22)	3	ANA, anti-dsDNA, anti-ssDNA
DeRycke <sup>17</sup> 2003	Belgium	AR 62 EA 35	38/24 12/23	54 (32-76) 47 (29-66)	RA, AS	—	AR 7.5 EA 8.5	ANA, anti-dsDNA, anti-histone, anti-nucleosome, anti-Sm, anti-RNP, anti-Ro, anti-La
Elkayam <sup>18</sup> 2005	Israel	26	17/09	51 (27-71)	RA	—	3	ANA, anti-dsDNA, aCL, ANCA, anti-RNP, anti-Sm, anti-Ro, anti-La, anti-SCL70, anti-peroxidase, anti-histone, total anti-ENA
Erikson <sup>19</sup> 2005	Sweden	53	43/10	55 (26-79)	RA	14 (2-37)	7.5 (3.5-13.5)	ANA, anti-dsDNA aCL, total anti-ENA, anti-nucleosome, anti-mitochondrial, anti-smooth muscle, anti-histone, anti-proteinase 3, anti-myeloperoxidase
Ferraro-Peyret <sup>20</sup> 2004	France	AR 24 EA 15	16/08 04/11	56 (26-77) 41 (26-57)	RA, AS	12 (3-32) 17 (6-30)	18	ANA, anti-DNAse aCL, anti-B2GPI, ANCA, anti-LKM, anti-mitochondrial, anti-smooth muscle, anti-peroxidase, anti-thyroglobulin, anti-adrenal
Hoxha <sup>21</sup> 2006	Italy	AR 30 EA 30	AR 24/06 EA 05/25	AR 52 (39-65) EA 35 (23-47)	RA, AS	AR 12 (05-18) EA 10 (02-18)	AR 29-53 EA 06-26	ANA, anti-dsDNA total anti-ENA
Jondosttir <sup>22</sup> 2004	Sweden	65	—	—	RA	—	12	aCL
Louis <sup>23</sup> 2003	Canada	42	05/37	53 (40-66)	RA, AS, PA	—	6	ANA, anti-dsDNA, anti-Sm, anti-Ro, anti-La, anti-RNP
Nancey <sup>24</sup> 2005	France	35	24/11	36 (19-71)	Crohn's	10 (03-24)	12	ANA, anti-dsDNA aCL, anti-B2GPI, anti-mitochondrial, anti-smooth muscle, anti-filaggrin, anti-LKM, anti-thyroid
Sellam <sup>25</sup> 2005	France	28	18/10	42 (28-56)	AS	10 (5-15)	8	ANA, anti-dsDNA, anti-histone, total anti-ENA
Vermeire <sup>26</sup> 2003	Bélgica	125	82/43	34 (28-43)	Crohn's	—	12	ANA, anti-dsDNA, anti-ssDNA, anti-histone, total anti-ENA
Total		760						

RA, rheumatoid arthritis; AS, ankylosing spondylitis; PA, psoriatic arthritis; ANA, antinuclear antibody; anti-dsDNA, anti-native or double-strand DNA; anti-ssDNA, Anti-Single Stranded DNA; aCL, anticardiolipin; ANCA, Anti-neutrophil cytoplasmic antibodies; anti-Beta2GP1, anti beta-2-glycoprotein-1 antibody; anti-ENA, Extractable Nuclear Antigen antibodies; anti-SCL70, anti-topoisomerase; anti-RNP, anti-ribonucleoprotein; anti-LKM, anti-liver-kidney microsome antibodies

**Table 2 – Variation of autoantibodies before and after infliximab use.**

Autoantibody	n	Before treatment	After treatment	Variation (%)
ANA	695	199 (28.6%)	469 (67.5%)	38.9
Anti-dsDNA	669	8 (1.2%)	117 (17.5%)	16.3
Total anti-ENA	351	0	0	0
aCL	222	21 (9.5%)	49 (22%)	12.5
Anti-beta 2 GP1	74	0	6 (8.1%)	8.1
Anti-histone	388	48 (12%)	116 (30%)	18
Anti-nucleosome	147	9 (6.1%)	22 (15%)	8.9
M ANCA	108	0	7 (6.5%)	6.5

ANA, antinuclear antibody; anti-dsDNA, anti-native or double-strand DNA; anti-ssDNA, Anti-Single Stranded DNA; anti-ENA, Extractable Nuclear Antigen antibodies; aCL, anticardiolipin; anti-Beta2GP1, anti beta 2 glycoprotein 1 antibody; ANCA, Anti-neutrophil cytoplasmic antibodies.

fore infliximab use ( $n = 74$  in two studies), but after using the medication, the variation was 6.5% (seven cases) (Table 2).

As for the anti-histone, it was evaluated by six studies (Table 1), with a total of 388 cases. Before the biological agent, 48 (12%) cases were reactive, but after the medication, 116 (30%) patients were reactive, within a variation of 18% (Table 2). In the study by Vermeire et al.,<sup>26</sup> no patient had anti-histone antibody before, but 1.6% of the cases (two in a total of 125) increased their titers and developed infliximab-induced lupus (IIL) after using infliximab for 24 months (in addition to the presence of anti-histone, there was also increase in the titers of ANA and anti-dsDNA). In 2004, Alanore et al.<sup>13</sup> evaluated the IgM and IgG isotypes separately, showing that, after using the medication, the IgM isotype increased significantly after 6 weeks, but with no clinical significance.

The anti-nucleosome antibody was assessed by two studies (Table 1), with a total of 147 cases, in which 9 (6.1%) were reactive before medication and 22 (26%) after the use of infliximab (Table 2), but with no clinical significance.

The anti-neutrophil cytoplasmic antibody (ANCA) was evaluated in three studies ( $n = 108$ ) (Table 1). Before infliximab, there were no cases of ANCA reactivity, with a variation of 6.5% (seven cases) after biological agent use (Table 2). There was no correlation with vasculitis in any of the cases. Eriksson et al.<sup>19</sup> in 2005, separately evaluated anti-proteinase 3 and anti-myeloperoxidase antibodies, but there was no reactivity in any case before or after the use of infliximab.

Four studies also evaluated other autoantibodies, namely: anti-mitochondrial, anti-smooth muscle, anti-fillagrin, anti-liver-kidney microsomal (anti-LKM), anti-peroxidase thyroid, thyroglobulin and anti-adrenal autoantibodies. None of the studies showed a significant variation in these antibodies. Of

the 760 cases evaluated in all studies, only 10 reported patients (1.3%) with probable IIL (Table 3).

## Discussion

This systematic review provides information on infliximab-induced autoantibodies and lupus erythematosus. The greatest difficulty in correlating autoantibodies is the lack of standardization, as each study used a different method. When the method used was the same, the autoantibody kits or ANA cut-offs were different, preventing a reliable comparison.

Our search included only phase-IV studies published from 2003 to 2006 (studies dating from previous years were excluded for not meeting the parameters used in this systematic review) (Figure 1). Viana et al.,<sup>27</sup> in 2010, performed a study in patients with psoriatic arthritis showing that anti-TNF therapy induced changes in ANA in one third of patients ( $n = 23$ ) and most evaluated autoantibodies (anti-nDNA, anti-Ro, anti-La, aCL, anti-histone and rheumatoid factor) did not react after biologic therapy. Although the study was well performed, we could not include it in this review, as the biological agents were evaluated together (infliximab, adalimumab and etanercept) and the results of patients using infliximab only were not reported (Fig. 1), although they were the majority (19 of 23 patients). The most recent study evaluated in our search was the one by Hoffmann et al.,<sup>28</sup> in 2011, regarding the use of infliximab in psoriasis. However, it could not be included in this review either, as some patients had used other biological agents before infliximab (Fig. 1), but were not separated from the total group, so we could not use their data in our calculations.

**Table 3 - Data of patients with infliximab-induced lupus erythematosus.**

Studies	Time after infliximab	Clinical signs	Autoantibodies	Evolution
Bobbio-Palavicinni <sup>14</sup>	30 weeks	Moderate arthritis and malar rash Pleuropericarditis	Anti-dsDNA Anti-dsDNA	Resolution a few weeks after withdrawal
Comby <sup>16</sup>	18 months	Migratory arthralgia, asthenia	ANA > 1:1280; anti-dsDNA IgG	Symptom duration for one month after infliximab withdrawal; control after corticosteroid; ANA remained persistently high
Elkayam <sup>18</sup>	3 infusions	Myalgia, arthralgia, fever > 38 °C, rash in the legs and arms	ANA, anti-histone	Resolution after infliximab and prednisone withdrawal
	5 infusions	Fever, myalgia, polyarthralgia	ANA, anti-histone	Infliximab and prednisone withdrawal for one week
Eriksson <sup>19</sup>		Myalgia, arthritis	Anti-histone, anti-dsDNA IgG, consumption of complements C3 and C4, leukopenia	Improvement after a few weeks of infliximab withdrawal without prednisone
Eriksson <sup>19</sup>	54 weeks	Malar rash, leukopenia, arthralgia and vasculitis in upper-limb distal extremities	Anti-dsDNA, anti-nucleosome	
Nancey <sup>24</sup>	3 infusions	Malar rash, polyarthralgia	ANA and anti-dsDNA	Spontaneous recovery after a few weeks without infliximab or corticosteroids
Vermeire <sup>26</sup>	1 infusion	Polyarthralgia, myalgia and malar rash	ANA, anti-dsDNA and anti-histone	Symptoms disappeared after infliximab withdrawal; reactive ANA even after a year, but with lower titers
	1 infusion	Arthralgia and malar rash	ANA 1:640	

ANA, anti-nuclear antibody; anti-dsDNA, anti-double-stranded DNA.



To calculate the percentage of autoantibodies found, we used as final result the period in which the antibodies were more reactive for studies that measured the antibodies several times during each visit, or, in the case of loss of patients, we used the period where there were more patients.

We chose studies of which duration was of at least three months, as there have been reports of this being the minimum time for autoantibody induction by infliximab.<sup>18,22</sup> However, Nancey et al.,<sup>24</sup> in 2005, showed that there has been persistent induction of ANA and anti-dsDNA even after the second infusion of the drug.

This systematic review found that the most common autoantibodies evaluated in the studies were ANA, anti-dsDNA, total anti-ENA and anti-histone. In fact, several studies chose to evaluate total anti-ENA and, in case of a reactive result, the autoantibodies would then be evaluated separately. However, as observed in our study that no patient reacted with the anti-ENA antibodies (n = 351) (Table 2), the number of patients that had these autoantibodies measured was lower than those who had other autoantibodies measured.

The autoantibody associated with antiphospholipid antibody syndrome (aCL) was described in 222 patients, but there was no clinical significance (no patient developed thrombotic episode). There were no cases of anti-Beta 2 GP 1 before infliximab use (n = 74 in both studies), but after using the medication, the variation was 6.5% (seven cases) (Table 2), also with no thrombotic events. The study of Bobbio-Palavicini et al.<sup>29</sup> in 2009 demonstrated a significant increase in anti-B2GP1 after infliximab use for 1-2 years, which did not happen with the other tested anti-TNF agents (etanercept and adalimumab). However, there was no association with clinical manifestations, either.

Regarding the development of autoimmune diseases, even for studies that showed a significantly higher ANA and other autoantibodies comparing the periods before and after infliximab, the latter did not induce any disease, except those 10 cases of IIL. In these patients, the most commonly found antibodies were ANA, anti-dsDNA and anti-histone, as demonstrated by several reports in the literature.<sup>30-32</sup> The most common clinical findings were arthralgia and myalgia, according to several case reports on this issue. Only one patient had serositis.

Autoantibody induction was not associated with the underlying disease, as the studies in this review evaluated patients with several autoimmune and inflammatory diseases (RA, AS, PA, Crohn's), generating multiple autoantibodies, regardless of the disease in question, but the non-development of other diseases suggests that it is only an epiphenomenon, and in most cases, these autoantibodies should not be pathogenic. Perhaps if methodologies that assessed more pathogenic antibodies were used, such as multiplex equipment, the result would be quite different. That is, we believe autoantibodies would be found in only a few cases.

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