Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: http://www.tandfonline.com/loi/ieds20

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To cite this article: Marta Pérez-De-Lis, Soledad Retamozo, Alejandra Flores-Chávez, Belchin Kostov, Roberto Perez-Alvarez, Pilar Brito-Zerón & Manuel Ramos-Casals (2017): Autoimmune Diseases Induced By Biological Agents. A review of 12731 cases (BIOGEAS Registry), Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2017.1372421

To link to this article: http://dx.doi.org/10.1080/14740338.2017.1372421

Accepted author version posted online: 31 Aug 2017.

Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Safety*

DOI: 10.1080/14740338.2017.1372421

Autoimmune Diseases Induced By Biological Agents

A review of 12731 cases (BIOGEAS Registry)

MARTA PÉREZ-DE-LIS[1], SOLEDAD RETAMOZO[2,3,4], ALEJANDRA FLORES-CHÁVEZ[2,5,6], BELCHIN KOSTOV[7], ROBERTO PEREZ-ALVAREZ[8], PILAR BRITO-ZERÓN[2,9], MANUEL RAMOS-CASALS[2,10,*]

AFFILIATIONS

[1]Servicio de Anestesiologia y Reanimación. Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain
[2]Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Barcelona, Spain
[3]Hospital Privado Universitario de Córdoba, Córdoba Argentina.
[4]Instituto De Investigaciones En Ciencias De La Salud (INICSA), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) - Córdoba - Argentina
[5] Unidad de Investigación Biomédica 02, Unidad de Investigación en Epidemiología Clínica, Centro Médico Nacional de Occidente (CMNO), Instituto Mexicano del Seguro Social (IMSS), Hospital de Especialidades, Guadalajara, Mexico.
[6]Programa de Doctorado en Ciencias Médicas, Centro Universitario de Investigaciones Biomédicas (CUIB), Universidad de Colima, Colima, Mexico.
[7]Primary Care Research Group, IDIBAPS, Barcelona, Spain.
[8]Department of Internal Medicine, Hospital Alvaro Cunqueiro, Vigo, Spain
[9]Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, Spain
[10]Department of Medicine, University of Barcelona, Barcelona, Spain

*See Appendix
**Alejandra Flores-Chavez holds a scholarship grant from the Mexican "Consejo Nacional de Ciencia y Tecnología (CONACyT)".

***Corresponding author:**
Phone: 34-93-2275774; FAX: 34-93-2271707; Email: mramos@clinic.cat

ABSTRACT

Introduction. Biological drugs are therapies designed to target a specific molecule of the immune system. Paradoxically, their use has been linked with the development or exacerbation of autoimmune disorders.

Areas covered. The BIOGEAS Registry currently collects information about nearly 13,000 reported cases of autoimmune diseases developed in patients exposed to biologics, including more than 50 different systemic and organ-specific autoimmune disorders, of which psoriasis (n=6375), inflammatory bowel disease (n=845), demyelinating CNS disease (n=803), interstitial lung disease (n=519), lupus (n=369), peripheral neuropathy (n=328), vasculitis (n=291) and hypophysitis (n=221) were the most frequently reported. The main biologics involved are anti-TNF agents in 9133 cases (mainly adalimumab in 4154, infliximab in 3078 and etanercept in 1681), immune checkpoint inhibitors in 913 (mainly ipilimumab in 524 and nivolumab in 225), B-cell targeted therapies in 741 (mainly rituximab in 678), and growth factor inhibitors in 549 cases (bevacizumab in 544). Even though targeting a particular immune molecule may be associated with an excellent clinical response in most patients, an unexpected autoimmune disease may arise in around 8 out of 10,000 exposed patients.

Expert Opinion. Following the increased use of biologics, the number and diversity of induced autoimmune disorders is increasing exponentially. For many of these drug-related processes, current treatment indications include the very biological agent producing the adverse event. Management of these biologic-induced autoimmune diseases will be an increasing clinical challenge in the daily practice in the next years.

Keywords: autoimmune disease, anti-TNF agents, rituximab, immune checkpoint inhibitors, growth factor inhibitors, cancer, big data, drug-induced event

Article highlights

- Nearly 13,000 cases of autoimmune disorders are reported in patients exposed to biological therapies.
- These disorders are reported overwhelmingly in patients with rheumatic diseases, cancer and IBD.
- There are more than 50 different biologic-induced systemic and organ-specific autoimmune disorders.
- Psoriasis, IBD, CNS demyelinating diseases, ILD and lupus were the most frequent induced autoimmune diseases
- The pharmacological scenario is highly heterogeneous with more than 30 different biological drugs involved pertaining to 8 different biologics groups
- The etiopathogenesis of these induced autoimmune diseases is unknown.
- A multidisciplinary workout is essential for managing the expected growing number of biological-induced autoimmune diseases.

1. Introduction

Biological therapies are used in a large number of rheumatic and autoimmune diseases, predominantly under specific license but also off-label. Although the majority of licensed drugs have demonstrated acceptable safety and tolerability profiles, autoimmune processes appearing after their use have increasingly been reported. During the last 10 years, we have investigated the characteristics of both systemic and organ-specific autoimmune disorders related to biological agents. In 2006, the Study Group on Autoimmune Diseases (GEAS) of the Spanish Society of Internal Medicine created the BIOGEAS project, a multicenter study devoted to collecting data on the use of biological agents in patients with autoimmune diseases. (1) In 2007, we published the first review of nearly 200 cases of systemic autoimmune diseases triggered by biological agents, overwhelmingly anti-TNF. (2) The most frequent induced diseases were lupus, vasculitis and sarcoidosis, and less-frequently, antiphospholipid syndrome and inflammatory myopathies. Subsequent reviews of the BIOGEAS Registry were published in 2010 (3) and 2013. (4)

The scenario of autoimmune diseases associated with the use of biologics has dramatically change in recent years due, on the one hand, to the increased number of biologics used in daily practice (5) and, in the other hand, by the emerging use of biologics in patients with solid cancers. (6) The purpose of this review is to update current knowledge on this topic based on the figures currently available in the last update of the BIOGEAS Registry.

2. Updated overview of the biogeas registry

Into the BIOGEAS project, a specific subproject of surveillance (BIOGEAS Registry) was designed to collect and analysed all the reported data on autoimmune diseases developed in patients exposed to biologics. A periodic surveillance of reported cases of autoimmune diseases triggered by licensed biological agents is carried out using a systematic Medline search. By May 31 2017, the number of cases of autoimmune disorders reported in patients exposed to biologics included in the BIOGEAS database is 12,731 (**Table 1**). Methodology is detailed in previous studies (2, 3). In this review, a further confirmation was made by excluding cases of a proven exacerbation of a previously known autoimmune disease.

2.1. Systemic diseases

a) Lupus

The Registry includes 369 cases of lupus induced by biological agents, overwhelmingly reported as isolated cases or series of cases in 123 out of 146 manuscripts (84%). The main

underlying disease identified was rheumatoid arthritis (RA) in 220 (60%) cases, followed by inflammatory bowel disease (IBD) (n=90), psoriasis/psoriatic arthritis (n=23) and spondyloarthropathies (n=14). The biologic administered consisted overwhelmingly in TNF-targeted therapies in 357 (97%), mainly infliximab (n=189), etanercept (n=85) and adalimumab (n=72). Rarely, lupus was associated with other biologics including bevacizumab (n=3), efalizumab (n=3), rituximab (n=2), ustekinumab (n=1) and ipilimumab (n=1).

With respect to the frequency of induced lupus, it reported in 85 out of 25363 patients exposed to biologics (0.33%) included in 16 studies (7–22) (**Table 2**); the frequency was higher in patients with RA (0.5%), patients who received infliximab (0.66% vs 0.49% for etanercept and 0.11% for adalimumab) and in retrospective studies (1% vs 0.44% in Pharmacovigilance studies and 0.05% in trials/prospective studies).

Specific characteristics of induced lupus were available in 221 cases, of whom only 66 (30%) fulfilled the current classification systemic lupus erythematosus (SLE) criteria. More than half of patients (n=119) present clinically with isolated cutaneous involvement, some presenting with infrequent cutaneous features such as lupus tumidus or childblain lupus.(23–25) Involvement of internal organs was very infrequent and included lupus nephritis (n=10), neurolupus (n=4) and pulmonary involvement (n=1). Some studies have suggested as potential risk factors for an enhanced risk of developing induced lupus pre-existing positive immunological markers (ANA, anti-DNA antibodies) or a family history of SLE. (9, 16, 26, 27).

b) Vasculitis

There are 291 cases of vasculitis induced by biological agents included in the Registry, overwhelmingly reported as isolated cases or series of cases in 85 out of 96 manuscripts (89%). The main underlying disease identified consisted of RA/Juvenile Idiopathic Arthritis (JIA) in 232 (80%) cases, followed by IBD (n=27) and psoriasis/psoriatic arthritis (n=10). The biologic administered consisted overwhelmingly in TNF-targeted therapies in 273 (94%), mainly etanercept (n=119) and infliximab (n=108). Isolated cases of vasculitis has been reported following the administration of other biologics including B-cell targeted therapies (rituximab in 4, alemtuzumab in 1), anticytokine therapies (tocilizumab in 2, ustekinumab in 1, daclizumab in 1), immune checkpoint inhibitors (ipilimumab in 3, pembrolizumab in 2) or growth factors inhibitors (bevacizumab in 2).

With respect to the frequency of induced vasculitis, it was reported in 106 (0.7%) out of 14444 patients (all with RA/JIA) exposed to biologics included in 7 studies (14, 17, 21, 28–31) (**Table 2**); the frequency was higher in patients who received etanercept and infliximab (0.82 and 0.76% vs 0.44% for adalimumab) and in retrospective studies (1.45%).
Specific clinical characteristics of induced vasculitis were available in 286 cases, of whom 187 (65%) present with isolated cutaneous involvement and 34 (12%) with isolated neurological involvement (peripheral neuropathy). Only 30 (10%) were classified as having a systemic vasculitis, mainly ANCA-related vasculitides in 12 cases, large-vessel vasculitides in 7 (4 GCA and 3 Takayasu arteritis), Henoch-Schonlein purpura in 7 and polyarteritis nodosa (PAN) in 3. ANCA were positive in 16 (18%) out of 95 tested patients (patterns were detailed in 9 cases, 5 pANCA and 4 cANCA).

c) Sarcoidosis

The Registry includes 139 cases of sarcoidosis induced by biological agents, overwhelmingly reported as isolated cases or series of cases in 100 out of 101 manuscripts. The main underlying disease identified was RA/JIA in 67 (48%) cases, followed by spondyloarthropathies (n=18), psoriasis/psoriatic arthritis (n=17) and melanoma (n=16). The biologic administered consisted overwhelmingly in TNF-targeted therapies in 111 (80%), mainly etanercept (n=58), adalimumab (n=27) and infliximab (n=25). Sarcoidosis was also reported in patients exposed to immune checkpoint inhibitors (ipilimumab in 13, nivolumab in 4), growth factors inhibitors (pembrolizumab in 3) and with rituximab (n=3), anakinra (n=2), tocilizumab (n=2), ustekinumab (n=1) and natalizumab (n=2).
Specific characteristics of induced sarcoidosis were available in 138 cases, of whom 91 (66%) presented involvement of an isolated organ and the remaining 47 (34%) involvement of two organs or more; the main involvements consisted of thoracic disease in 97 (70%) cases and cutaneous involvement in 49 (35%).

d) Other systemic diseases

There are 51 reported cases of induced RA/polyarthritis associated with the use of biologics, including the recent study by Belkhir et al (32) of 6 cases of RA developed after treatment with anti-programmed death-ligand 1 (PD1) agents (nivolumab and pembrolizumab. Other induced diseases reported included inflammatory myopathies (n=32), hemophagocytic lymphohistiocytosis (HLH) (n=16), antiphospholipid syndrome (APS) (n=9) or polymyalgia

rheumatica (PMR) (n=8). A recent study by Le Burel et al (33) has reported 30 new cases of systemic diseases related to the use of immune checkpoint inhibitors.

2.2. Cutaneous diseases

a) Psoriasis

Psoriasis is another example of the paradoxical relationship between biological agents and diseases for which their use is licensed. The Registry includes 6375 cases of psoriasis induced by biological agents, mainly reported as isolated cases or series of cases (69 out of 94 manuscripts, 73%). The main underlying diseases identified consisted of IBD in 513, RA/JIA in 237 cases and spondyloarthropathies in 84; in the largest series published by Kip et al (34), including 5432 cases, underlying diseases were not detailed. The biologic administered consisted overwhelmingly in TNF-targeted therapies in 6337 (99%) cases, mainly adalimumab (n=3720) and infliximab (n=2320). Rarely, psoriasis was developed following the administration of other biologics, mainly rituximab in 18 cases.

The frequency of psoriasis was evaluated in 20 studies (13, 15, 30, 35–51): 385 (1.34%) out of 28734 patients exposed to biologics developed psoriasis (**Table 2**). The frequency was higher in patients with JIA (2.49%) or IBD (2.1%), and in patients exposed to infliximab (1.4% vs 1.29% for adalimumab and 0.19% for etanercept).

b) Alopecia

The Registry includes 139 reported cases of autoimmune alopecia (mostly reported as alopecia areata) arising in patients exposed to biological agents, mainly treated for RA/JIA (38 cases), psoriasis (31 cases) and IBD (28 cases). The biologic administered consisted overwhelmingly in TNF-targeted therapies in 126 (91%), including infliximab (n=56), adalimumab (n=41) and etanercept (n=29). Rarely, alopecia was reported following the administration of other biologics, including pembrolizumab (n=3), nivolumab (n=3) and ipilimumab (n=1).

c) Other cutaneous diseases

The list of other cutaneous diseases induced by biological agents is wide, with vitiligo (n=54) and lichen (n=44) being the most frequently reported; other cutaneous diseases less frequently reported included hidradenitis suppurativa (n=29), granuloma annulare (n=19), pyoderma gangrenosum (n=12) or Sweet's syndrome (n=7).

2.3. Neurological diseases

a) Central nervous system demyelinating diseases

The Registry includes 803 reported cases of central nervous system (CNS) demyelinating diseases in patients exposed to biologics, overwhelmingly reported as isolated cases or series of cases in 76 out of 85 manuscripts (89%). The underlying diseases were detailed in only 184 cases (in the largest series the underlying disease was not detailed), and the most frequent were RA/JIA in 66 (36%) and IBD in 66 (36%). The biologic administered consisted overwhelmingly in TNF-targeted therapies in 740 (92%), mainly etanercept (n=384) and infliximab (n=257). Rarely, CNS demyelinating disease was developed following the administration of other biologics, mainly growth factors inhibitors (bevacizumab in 7) or immune checkpoint inhibitors (ipilimumab in 5).

CNS demyelinating diseases were diagnosed in 13 (0.03%) out of 39933 patients exposed to biologics included in 5 studies (52–56) (**Table 2**). Specific characteristics of induced demyelinating diseases were available in 651 cases, of whom 254 were classified as multiple sclerosis (MS)/MS-like and 523 as neuromyelitis optica (NMO) (504 as isolated optic neuritis, 17 as isolated myelitis and only 2 as neuromyelitis); most of the reported cases of optic neuritis were included in the study of Winthrop et al (55) who reported 358 cases of optic neuritis in new users of anti-TNF therapies in US between 2000 and 2007.

b) Non-demyelinating diseases

The Registry includes 57 cases of non-demyelinating CNS disorders induced by biologics, mainly in patients treated for RA, IBD and psoriasis. These patients were exposed mainly to anti-TNF agents (42 cases, including infliximab in 19, etanercept in 13 and adalimumab in 10), but also in patients treated with bevacizumab in 10 cases. There is a wide spectrum of neurological diseases reported, with diffuse encephalopathy being the most frequent (n=41) followed by focal motor deficits (n=6) and cerebellous ataxia (n=3).

c) Cranial nerves involvement

The Registry includes 104 cases of involvement of cranial nerves related to the administration of biologic drugs, mainly in patients with underlying rheumatic diseases (n=86, 83%). The biologic administered consisted overwhelmingly in TNF-targeted therapies in 99 (95%), mainly etanercept (n=59) and infliximab (n=31), with 5 additional cases recently reported related to ipilimumab. One study (57) reported one case out of 752 patients with melanoma treated with ipilimumab. The majority of cases consisted of facial palsy

(n=99) and were included in the study by Deepak et al (58) who evaluated neurological adverse events reported to the Food and Drug Administration Adverse Event Reporting System (FAERS) (January 1, 2000 to December 31, 2009) in patients exposed to infliximab, adalimumab, certolizumab and etanercept.

d) Polyradiculopathies

Induced polyradiculopathies (mainly acute and chronic idiopathic polyradiculopathy) were reported in 96 cases, mainly in patients with RA/JIA (n=40). The biologic administered consisted in TNF-targeted therapies in 78 (81%) cases, mainly infliximab (n=43). Tsouni et al (59) reported 7 (0.3%) cases out of 2017 patients exposed to anti-TNF therapies.

e) Peripheral neuropathies

Of the 328 reported cases of induced peripheral neuropathies reported in patients exposed to biologics, 297 were included in the pharmacovigilance study published by Deepak et al (58). The majority of cases were reported in patients with rheumatic diseases and IBD. The biologic administered consisted overwhelmingly in TNF-targeted therapies in 311 (95%) cases, mainly infliximab (n=133) and etanercept (n=119). Tsouni et al (59) reported 3 (0.14%) cases out of 2017 patients exposed to anti-TNF therapies.

f) Neuromuscular diseases

The Registry includes 14 reported cases of myasthenia, mainly related to the use of immune checkpoint blocking agents including either anti-CTL4 (ipilimumab, 4 cases) and anti-PD1 (nivolumab in 4, pembrolizumab in 3) agents, used overwhelmingly in patients with cancer (12 cases including 7 patients with melanoma).

2.4. Digestive diseases

a) Inflammatory Bowel Disease

Another paradoxical example of autoimmune diseases induced by biologics is the development of IBD, one of the diseases with the highest rates of use of biologics. The Registry includes 845 cases of IBD induced by biologics, mainly reported as isolated cases or series of cases in 32 out of 53 manuscripts (60%). Induced IBD consisted of Chron's disease in 355 cases and ulcerative colitis in 228; in the remaining cases, the disease was classified as non-specific colitis or as non-classified IBD. Underlying diseases were specified in 451 cases and the most frequently reported was RA/JIA in 265 (59%) cases. The biologics

administered consisted overwhelmingly in TNF-targeted therapies in 716 (85%) cases, mainly etanercept in 648 cases (443 of which were included in the study by O'Toole et al (60). IBD has been also recently associated with the use of the new immune checkpoint inhibitors, mainly with ipilimumab in 98 cases.

Induced IBD was reported in 79 (0.71%) out of 11173 patients included in 13 studies (30, 40, 51, 61–70) (**Table 2**); the frequency was higher in patients treated for melanoma (1.1%) and those exposed to etanercept (0.81% vs 0.29% for infliximab and 0.07% for adalimumab).

b) Autoimmune hepatitis

The Registry includes 122 cases of autoimmune hepatitis induced by biologics, mainly reported as isolated cases or series of cases in 49 out of 55 manuscripts (89%). The main underlying disease consisted of melanoma in 42 cases, and the biologics administered were TNF-targeted therapies in 64 (52%) cases, mainly infliximab (n=52). Hepatitis has been also reported following the administration of anti-CTL4 agents (n=28) anti-PD1 agents (n=16) and natalizumab (n=11).

c) Autoimmune pancreatitis

Flaig et al (71) have recently reported 53 cases of tocilizumab-induced pancreatitis, 52 of which were collected from a review of data from the FAERS. Recent studies have also linked pancreatitis with the use of checkpoint (3 nivolumab, 1 ipilimumab) and growth factors (7 pembrolizumab) inhibitors (51, 72, 73).

2.5. Hematological diseases

a) Neutropenia

Neutropenia is the cytopenia more frequently related with the administration of biological agents, with nearly 1000 reported cases. The frequency of neutropenia was evaluated in 83 studies (69, 74–155) including 9853 patients and was reported in 830 (8.4%); the frequency was higher in patients with underlying solid neoplasia (30.3%), patients who received organ transplantation (13.2%) and in those with hematological neoplasia (11.7%) and melanoma (11.3%). The biologics associated with the highest frequencies of induced neutropenia were ipilimumab (33%), bevacizumab (32.7%), nivolumab (9.9%) and tocilizumab (9%).

b) Thrombocytopenia

Thrombocytopenia was reported in nearly 500 cases. Neutropenia was reported in 395 (9.6%) out of 4113 patients exposed to biologics included in 48 studies (63, 69, 76, 77, 81, 86–89, 96, 102, 104, 105, 109, 112, 119, 125, 129, 130, 132, 134, 143, 149, 150, 156–179); the frequency was especially higher in patients with underlying solid neoplasia (23.8%) and in those with melanoma (12.8%) or hematological neoplasia (10.7%). The biologics with the highest frequencies of induced thrombocytopenia were bevacizumab (27.3%), ipilimumab (23.5%), daclizumab (16.9%) and rituximab (9.5%).

c) Hemolytic anemia

Hemolytic anemia was reported in 34 cases. The frequency of haemolytic anemia was evaluated in 4 studies (165, 174, 180, 181) including 699 patients and was reported in 14 (2%). The main underlying diseases identified consisted of patients who received transplantation (n=10) and those with hematological neoplasia (n=6) and melanoma (n=5). The biologic administered included alemtuzumab (n=12), nivolumab (n=5), ipilimumab (n=4), infliximab, rituximab, natalizumab and bevacizumab (2 cases each) and adalimumab, etanercept, daclizumab and eculizumab (1 case each).

d) Eosinophilic diseases

Eosinophilic diseases were reported in 36 cases, mainly in patients with psoriasis/psoriatic arthritis (n=11), RA/JIA (n=7) and MS (n=6). The biologic administered consisted of TNF-targeted therapies in 26 (72%) cases, mainly adalimumab (n=10) and infliximab (n=7). Other biologics involved included natalizumab (n=6), ustekinumab (n=2), ipilimumab (n=2), anakinra (n=1), daclizumab (n=1), tocilizumab (n=1), nivolumab (n=1) and pembrolizumab (n=1). The main clinical presentations included peripheral eosinophilia in half the cases (n=19), eosinophilic pneumonia (n=6) and eosinophilic cellulitis/fasciitis (n=6).

2.6. Respiratory diseases

a) Interstitial lung disease

Interstitial lung disease (ILD) is a known side effect of various drugs (182), including biological agents. The Registry includes 519 cases of ILD arising in patients exposed to biological agents, overwhelmingly reported as isolated cases or series of cases in 103 out of 121 manuscripts (85%). The main underlying diseases were neoplasia, either hematological (n=160) or solid (78 cases of melanoma, 68 of lung cancer), and RA/JIA (n=100). Three main groups of biologics are associated with the development of ILD:

a) B-cell targeted therapies (rituximab) in 183 cases, 121 of which were included in the review by Hadjinicolaou *et al.* (183), nearly all reported in patients with haematological malignancies, with only 7 cases reported in patients with autoimmune diseases.
b) Immune checkpoint inhibitors in 177 cases, mainly nivolumab (82 cases) and pembrolizumab (35 cases), most included in a review of trials recently published by Nishino et al)(184)
c) TNF-targeted therapies in 139 patients, mainly related to exposure to etanercept (n=61), and infliximab (n=60); the majority of cases were included in two Japanese pharmacovigilance studies: 42 of the 61 cases of etanercept in the study by Koike et al (185) and 25 of the 60 cases of infliximab in the study by Takeuchi et al (186).

Although most cases were reported as ILD, pneumonitis or pulmonary fibrosis, in some cases the diagnosis of induced ILD was more specific including patients who developed usual interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia or alveolar haemorrhage.

Induced ILD was reported in 249 (1.6%) out of 15079 patients exposed to biologics evaluated included in 17 studies (57, 183, 186–199) (**Table 2**); the frequency was higher in patients who received nivolumab (3.0%), bevacizumab (2.1%) and, especially, in those treated with the combination of nivolumab and ipilimumab (6.9%).

b) Other respiratory diseases

Isolated cases of other respiratory diseases have also been reported including eosinophilic pneumonia (n=6), hypersensitivity pneumonia (n=4) or sinusitis (n=2).

2.7. Endocrine diseases

a) Hypophysitis

The Registry includes 221 reported cases of induced hypophysitis in patients treated with biological agents, mainly included in randomized controlled trials (RCTs) (29 out of 63 manuscripts). All cases included patients treated for cancer (overwhelmingly patients with melanoma, 198 out of the 221 cases) (90%). The biologic administered in almost all the cases was the immune checkpoint inhibitor ipilimumab in 213 (96%) cases, with isolated reported cases related to the administration of nivolumab (n=4), pembrolizumab (n=2) and tremelimumab (n=2).

Induced hypophysitis was reported in 164 (2.95%) out of 5556 patients included in 37 studies (51, 57, 77, 86, 118, 200–231)(**Table 2**); the frequency was higher in patients with melanoma (3.3%) and those exposed to ipilimumab (3.81%).

b) Thyroiditis

There are 59 cases of induced thyroiditis reported in patients exposed to biologics, 36 of which included in two studies (203, 232). All patients but 2 (with RA, treated with etanercept) had an underlying cancer, mainly melanoma (n=38), treated with immune checkpoint inhibitors, including ipilimumab (n=31), nivolumab (n=13) and pembrolizumab (n=13).

c) Other endocrine diseases

The Registry collected other induced endocrine diseases including new onset of type I diabetes mellitus (n=27), adrenalitis (n=16) and hypoparathyroidism (n=1).

2.8. Ocular diseases

a) Uveitis

There are 182 cases of uveitis induced by biological agents, mainly reported as isolated cases or series of cases in 21 out of 32 manuscripts (66%). The main underlying disease identified consisted of RA/JIA in 125 (69%) cases. The biologic administered consisted overwhelmingly of TNF-targeted therapies in 166 (91%), mainly etanercept (n=141). Rarely, uveitis was developed following the administration of immune checkpoint inhibitors, mainly ipilimumab (n=9) and pembrolizumab (n=5).

Induced uveitis was reported in 107 (1.98%) out of 5391 patients exposed to biologics included in 8 studies (30, 40, 57, 66, 233–236)(**Table 2**); the frequency was higher in patients with JIA (2.5%), in patients who received adalimumab (4.3%) or etanercept (2.2%), and lower in those treated with infliximab (1.1%).

b) Other inflammatory ocular diseases

Other iinflammatory ocular disease may also arise after initiation of biological therapies: we have identified 30 cases, including scleritis (n=10) retinal thrombosis (n=6) orbital inflammation (n=4) ulcerative keratitis (n=3), Vogt-Koyanagi-Harada syndrome (n=3) endophthalmitis (n=2)

central serous retinopatyhy (n=1) and macular edema (n=1). These ocular diseases appeared mainly in patients with underlying RA (n=11) or melanoma (n=9), and were mainly related to the use of anti-TNF (n=18) or ipilimumab (n=8).

2.9. Kidney diseases

a) Glomerulonephritis

The Registry includes 50 cases of glomerulonephritis (GN) induced by biological agents, mainly reported as isolated cases or series of cases in 31 out of 34 manuscripts (91%). The main underlying diseases consisted of cancer in 19 cases (mainly melanoma in 7 and lung cancer in 6) and RA in 14 cases. The biologic administered consisted mainly of TNF-targeted therapies in 25 (50%) cases, including etanercept (n=11), adalimumab (n=8) and infliximab (n=6). GN was also reported following the administration of bevacizumab (n=9) and ipilimumab (n=5). Among patients in whom histopathology was detailed, the most frequent types of GN consisted of rapidly-progressive GN (n=10), membranous GN (n=8) and IgA GN (n=5).

b) Interstitial nephritis

There are 22 reported cases of acute tubulointerstitial nephritis (ATIN) in patients exposed to biologics. The main underlying diseases identified consisted of cancer in 16 cases (mainly lung cancer in 7 and melanoma in 6). The biologic administered consisted mainly in immune checkpoint inhibitors including nivolumab (n=7), pembrolizumab (n=4) and ipilimumab (n=3), bevacizumab (n=2), and TNF-targeted therapies in the remaining 5 (mainly infliximab in 4).

2.10. Cardiovascular diseases

There are 13 cases of pericarditis and 1 case of myocarditis included in the Registry.

3. Expert opinion

The BIOGEAS Registry currently includes nearly 13,000 cases of more than 50 different systemic and organ-specific autoimmune disorders reported in patients exposed to biological therapies. Although most cases come from retrospective studies and isolated case reports (a fact probably related to the very low prevalence of these induced processes), several controlled trials and large postmarketing studies have been published in recent years. Paradoxically, for many of these drug-related autoimmune diseases, current treatment

indications include the very biological agent producing the adverse event and therefore, these disorders are reported overwhelmingly in patients with diseases for which biologics are licensed and extensively used: rheumatic diseases (mainly RA), cancer (mainly melanoma) and IBD. (**Table 3**)

Our first publication in 2007 (2) included 233 cases of autoimmune diseases (vasculitis in 113, lupus in 92, ILD in 24, and other diseases in 4) in patients exposed to TNF-targeted therapies. In 2010 (3), we reviewed more than 800 cases and, in the last review of the Registry published in 2013 (4), more than 1500 cases. With nearly 13,000 cases now included in the Registry, we confirm the exponential growing number of reported cases (a figure that has been multiplicated by 60 in only 10 years). Not only the number of cases has exponentially grown, but also the pharmacological scenario is much more heterogeneous now with more than 30 different biological drugs involved pertaining to 8 different biologics groups (**Table 4**), with a continuous report of new drugs involved year by year (**Figure 1**). The scenario of is also much more diverse with respect to the underlying diseases of patients exposed to biologics (**Table 5**) (**Figure 2**), a fact clearly related to the increasing use of immune checkpoint inhibitors (**Figure 3**), including those targeting the programmed cell death 1/programmed cell death ligand 1 and cytotoxic T lymphocyte antigen 4 pathways, which have dramatically changed the therapy of cancer.(237) Treatment with these novel immunotherapies has resulted in a highly-specific spectrum of autoimmune adverse events (238), especially with respect to endocrine diseases.

Psoriasis, IBD, CNS demyelinating diseases, ILD and lupus were the most frequent induced autoimmune diseases included in the BIOGEAS Registry, a scenario clearly different from that reported 10 years ago (**Figure 4**); in addition, a differentiated pattern of association with the different groups of biologics is clearly evident disease by disease (**Figure 5**). However, the level of association between a drug and the induced autoimmune disease cannot be evaluated by a global analysis of individual reported cases and should always be studied according to the estimated total population exposed to this agent. According to the data included in these studies (**Table 2**) allows the estimated frequency of induced autoimmune diseases is around 8 cases per 1000 patients exposed to biologics. However, the figures may vary widely according to the induced autoimmune disease, the design of the studies, the biological agent involved or the underlying disease of exposed patients.

The etiopathogenesis of these induced autoimmune diseases is unknown. Probably, a specific genetic background that predispose to their development may play a key role. This could also contribute to explain the exacerbations of pre-existing autoimmune diseases reported in

patients exposed to biologics (a clinical situation not specifically analysed in this review). Furthermore, it seems reasonable to hypothesize that patients with pre-treatment positive immunological markers could be more prone to develop autoimmune processes, as has been reported in patients with RA. In addition, some patients could have abnormalities in CD4+CD25+ regulatory T-cell function, a subset of T-cells that play a key role in controlling the development of autoimmune processes (239). However, further studies should be focused on searching for specific etiopathogenic mechanisms that could clearly link the induced autoimmune disorder with the immunological pathways altered by the biological drug administered, since for some reported clinical scenarios other etiopathogenic mechanisms have been proposed. In some cases, differentiation between an allergic reaction to the drug and a true induced autoimmune disease may be difficult. Some patients may develop a systemic drug-induced syndrome (asthenia, general malaise, fever, non-specific cutaneous rashes or purpura, arthralgia and/or myalgia); this clinical presentation, together with the induction of ANA/anti-dsDNA by biologics (mainly by anti-TNF agents), may result in a lupus/vasculitic-like presentation of a systemic drug reaction that cannot be classified as a true drug-induced SLE/systemic vasculitis. In other cases, the induced autoimmune complication is a frequent organ-specific involvement included into the clinical spectrum of the underlying disease, and arise "per se" and not because of the use of the biological drug. The best example is the development of uveitis in patients with spondyloarthropathies exposed to biologics: Wendling *et al.* (240) reported in some patients the development of uveitis in spite of having a successful articular response to the anti-TNF therapy, and the resolution in most cases of the induced uveitis when the anti-TNF agent was continued, suggesting differing etiopathogenic pathways of the ocular and articular inflammations in response to TNF blockade. (241)

With respect to the prognosis, in previous reviews of the Registry we reported that most of cases related to TNF-targeted therapies appeared between one month and one year after initiation of the biological agent, with a complete resolution of nearly 75% of cases after cessation of therapy (although the prognosis was worse in some specific involvements such as interstitial lung disease, inflammatory ocular disease and central nervous system demyelinating diseases) (2–4, 241–243). With respect to the new anticancer biological drugs, it seems that the prognosis of the induced autoimmune events may follow a similar profile, since if it are diagnosed timely, the majority of events are completely reversible, requiring the use of immunosuppressive agents only in limited cases. (244) The appearance of new biologics targeting other molecules is being providential, as it could increase the number of

agents that we could use to control the underlying disease in place of the agent causing the induced autoimmune disorder.

Finally, the design of the BIOGEAS Registry (descriptive collection of reported cases) has some limitations. It is important to note that we cannot discard a potential role of other concomitant drugs in the etiopathogenesis of the induced autoimmune disease. In addition, although the great majority of reported cases defined the induced autoimmune disease as newly diagnosed, in some cases this was not clearly stated. Some patients had also two or more coexisting induced autoimmune diseases, so the total number of cases reported is not exactly the total number of patients reported (although this accounted for less than 1% of cases). And with respect to the number of reported cases, it should consider that the total figure could be strongly influenced by the existence or not of pharmacovigilance national studies in which the number of identified cases is often large (**Supplementary Figure 1**). In spite of these limitations and the limited quality of the available data (overwhelmingly based on uncontrolled studies), most of the previously reported recommendations for the management of patients with autoimmune diseases triggered by biological agents remain valid (4). Before initiating the biological therapy, a careful pre-therapeutic evaluation paying special attention to pre-existing clinical or immunological autoimmune features is recommended. When the autoimmune disease appears, a careful evaluation of non-specific symptoms (asthenia, fever, cutaneous rashes, arthromyalgia) is highly recommended. Discontinuation of biological therapy is mandatory in patients with severe involvement of internal organs and recommended in patients with milder features, in whom continuation could also be considered (always with a closer follow-up) if biological therapy is considered essential to control the underlying disease. Corticosteroids and/or immunosuppressive agents may be required in severe cases to control the induced autoimmune disease despite the withdrawal of the biological agent. Once the induced autoimmune disease is resolved and to control the active underlying disease, restarting biological treatment with a different class of agent (whenever possible) may be a reasonable option.

4. Conclusion

Biological agents have emerged as effective therapies for treating a widening spectrum of diseases. An emerging number and variety of autoimmune adverse events are reported, ranging from asymptomatic immunological alterations to life-threatening systemic autoimmune diseases. Paradoxically, for many of these drug-related autoimmune processes, current treatment indications include the very biological agent producing the adverse event.

Available data on the amount of reported cases and the clinical significance of these autoimmune induced disorders rely on some RCTs but especially on many observational studies and a very large number of isolated case reports. It will be essential for clinicians to continuously update their knowledge on these adverse events for an early diagnosis and correct management of these events. The future focus of research should be directed to identify potential high-risk subsets of patients by means of specific genetic or biological markers that could predict the risk of developing these autoimmune adverse events. A multidisciplinary workout is essential, with a central role for the specialist in autoimmune diseases who should get used to manage not only the "spontaneous" autoimmune diseases, but also the expected growing number of these biological-induced autoimmune diseases.

Funding
This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

APPENDIX. The members of the *Spanish Study Group of Biological Agents in Autoimmune Diseases* (BIOGEAS) of the *Spanish Society of Internal Medicine* (SEMI) involved in this review were:

Pilar Brito-Zerón[1,2], Roberto Pérez-Alvarez[3], Belchin Kostov[4], Nihan Acar-Denizli[5], Antoni Sisó-Almirall[4], Alejandra Flores-Chavez[2], Soledad Retamozo[6], Sofía Arteaga[2], Hoda Gheitasi[2], César Morcillo[1], Lucio Pallarés[7], María-José Cuadrado[8], Munther A. Khamashta[8], Marta Pérez-de-Lis[9], Manuel Ramos-Casals[2,10]

(1) Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, Spain
(2) Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Barcelona, Spain
(3) Department of Internal Medicine, Hospital Alvaro Cunqueiro, Vigo, Spain
(4) Primary Care Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Primary Care Centre Les Corts, CAPSE, Barcelona, Spain
(5) Department of Statistics, Faculty of Science and Letters, Mimar Sinan Fine Arts University, Istanbul, Turkey
(6) Servicio de Reumatología, Hospital Privado Universitario de Córdoba, Córdoba, Argentina.
Instituto De Investigaciones En Ciencias De La Salud (INICSA), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) - CORDOBA - Argentina.
(7) Systemic Autoimmune Diseases Unit, Department of Internal Medicine, Hospital de Son Espases, Palma de Mallorca, Spain
(8) Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, King's College University, London, UK
(9) Servicio de Anestesiologia y Reanimación. Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain
(10) Department of Medicine, University of Barcelona, Barcelona, Spain

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Table 1. List of systemic and organ-specific autoimmune diseases reported in patients exposed to biological agents: eaBIOGEAS Registry (uptade May 31, 2017)

CLASSIFICATION	REPORTED CASES (n)
Systemic diseases	
Lupus	369
Vasculitis	291
Sarcoidosis	139
RA/polyarthritis	51
Inflammatory myopathies	32
HLH	16
Other diseases	59
Cutaneous diseases	
Psoriasis	6375
Alopecia	139
Vitiligo	54
Lichen	44
Other diseases	86
Neurological diseases	
CNS demyelinating diseases	803
Peripheral neuropathies	328
Cranial nerve involvement	104
Polyradiculopathies	96
CNS other diseases	57
Neuromuscular diseases	14
Digestive diseases	
Inflammatory bowel disease	845
Autoimmune hepatitis	122
Autoimmune pancreatitis	64
Hematological diseases	
Neutropenia	965
Thrombocytopenia	461
Hemolytic anemia	34
Eosinophilia/hypereosinophilic diseases	36
Respiratory diseases	
ILD	519
Sinusitis	2
Hypersensitivity pneumonitis	4
Endocrine diseases	
Hypophysitis	221
Thyroiditis	59
Diabetes	27
Adrenalitis	16
Hypoparathyroidism	1
Ophthalmological diseases	
Uveitis	182

▯ Other diseases	30
Kidney diseases	
▯ Glomerulonephritis	50
▯ Acute tubulointerstitial nephritis	22
Cardiovascular diseases	
▯ Pericarditis	13
▯ Myocarditis	1

Table 2. Frequency of the main induced systemic and organ-specific autoimmune diseases in patients exposed to biological agents: BIOGEAS Registry (uptaded May 31, 2017)

Induced disease	Number of studies (n)	Patients exposed (n)	Patients with induced disease (n)	Cases per 1000 patients exposed (‰)
Hypophysitis	39	5,556	164	29,52
Uveitis	8	5,391	107	19,85
ILD	17	15,079	249	16,51
Psoriasis	20	28,734	385	13,40
Vasculitis	7	14,444	106	7,34
IBD	14	11,173	79	7,07
Lupus	16	25,363	85	3,35
CNS demyelinat.	5	39,933	13	0,33
TOTAL	**126**	**145,673**	**1,188**	**8,16**

TABLE 3. Underlying diseases classified per group of disease: data available in 12295 cases (in 436 cases, data were not detailed or consisted of mixed data).

Group of diseases	N	%
Rheumatic diseases	8932	72,65
Solid cáncer	1611	13,10
IBD	936	7,61
Hematological neoplasia	427	3,47
Cutaneous diseases	124	1,01
SAD	111	0,90
Transplantation	60	0,49
Neurological diseases	52	0,42
Other autoinmune diseases	36	0,29
Rare diseases	6	0,05

TABLE 4. List of the reported biologics involved in the development of induced autoimmune diseases (BIOGEAS Registry, update May 31, 2017).

	Molecule	Cases (n)
a) TNF-targeted therapies		**9133**
- Adalimumab	*TNF*	4154
- Infliximab	*TNF*	3078
- Etanercept	*TNF*	1681
- Certolizumab	*TNF*	198
- Golimumab	*TNF*	20
- Lenercept	*TNF*	2
b) B-cell targeted therapies		**741**
- Rituximab	*CD20*	678
- Alemtuzumab	*CD52*	62
- Blinatomumab	*CD19*	1
- Epratuzumab	*CD22*	0
c) Anticytokine therapies		**285**
- Tocilizumab	*IL6*	224
- Daclizumab	*IL2*	25
- Anakinra	*IL1*	18
- Ustekinumab	*IL12/IL23*	17
- Canakinumab	*IL1*	1
d) Checkpoint inhibitors		**913**
- Ipilimumab	*CTL4*	524
- Tremelimumab	*CTL4*	2
- Nivolumab	*PD1*	225
- Pembrolizumab	*PD1*	162
e) Growth factors-targeted agents		**549**
- Bevacizumab	*EGFR*	544
- Cetuximab	*EGFR*	2
- Gefitinib	*EGFR*	1
- Osimertinib	*EGFR*	1
- Panitumumab	*EGFR*	1
f)) Other biological drugs		**60**
- Natalizumab	*a4 integrin*	27
- Efalizumab	*CD11a*	16
- Abatacept	*CD28*	14
- Eculizumab	*C5*	3

TABLE 5. Underlying diseases were detailed in 5061 cases: Top 10 of the most frequently reported diseases

	N	%
1. Rheumatoid arthritis	1644	32,48
2. IBD	936	18,49
3. Melanoma	774	15,29
4. B-cell lymphoma	350	6,90
5. Lung cancer	285	5,63
6. Ankylosing spondylitis	243	4,80
7. Psoriasis/PsA	210	4,15
8. Colorectal cancer	158	3,12
9. Ovarian cancer	90	1,78
10. Pancreatic cancer	57	1,13

FIGURES

Figure 1. Cumulated number of cases per year of biologics involved in induced autoimmune diseases. Only biologics with > 10 reported cases are included. Pharmacovigilance studies were excluded.

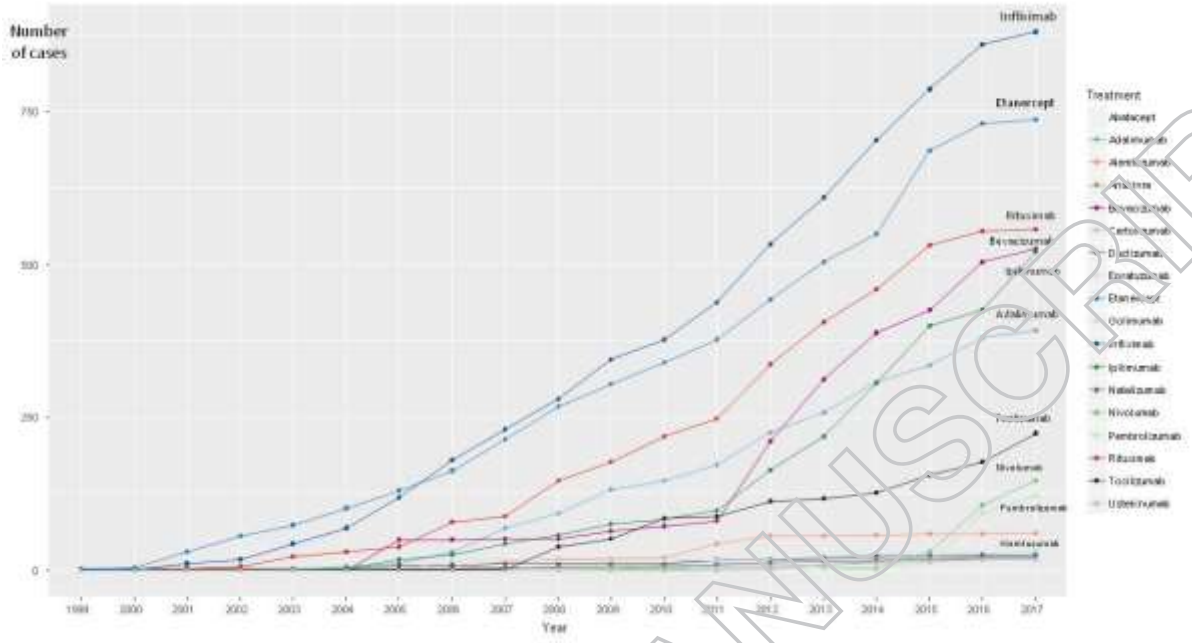


Figure 2. Underlying diseases of patients exposed to biologics included in the BIOGEAS Registry (2007 vs 2017)

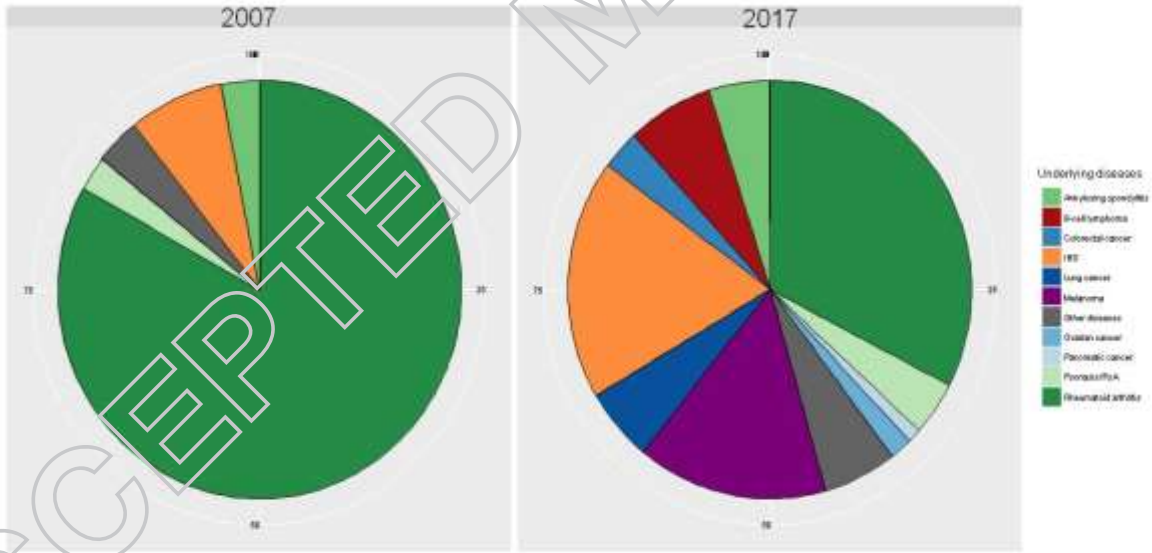


Figure 3. Cumulated number of cases per year of biologics involved in induced autoimmune diseases classified per groups (TNF-targeted, immune checkpoint/growth factors inhibitors, B-cell targeted and others). Only biologics with > 10 reported cases are included. Pharmacovigilance studies were excluded.

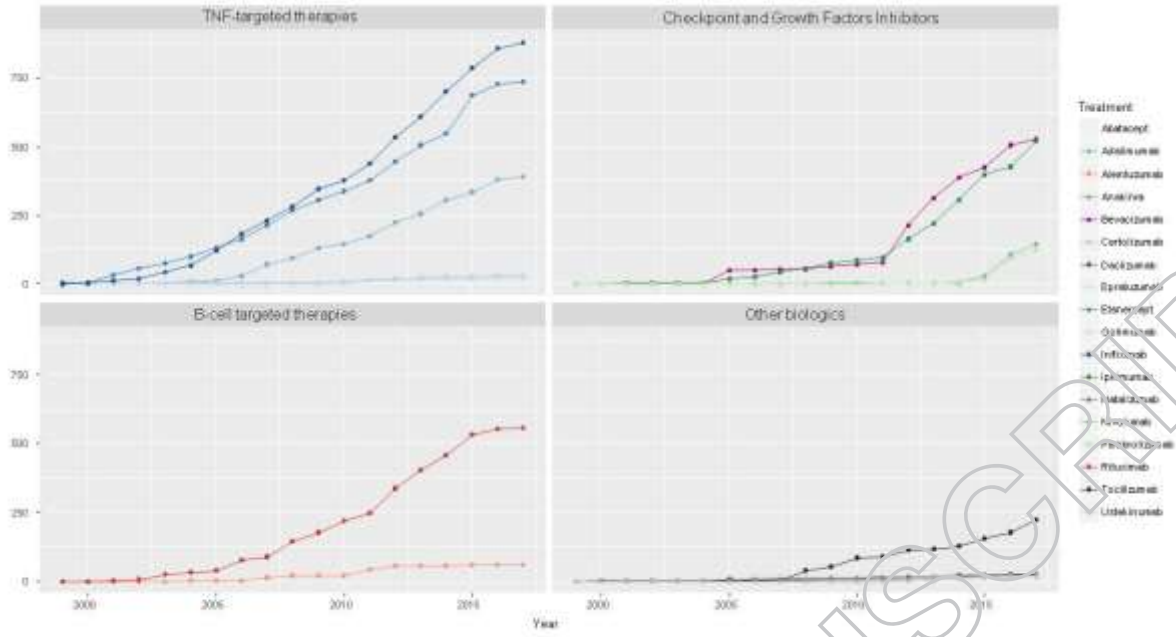


Figure 4. Main biologic-induced autoimmune diseases included in the BIOGEAS Registry (2007 vs 2017)

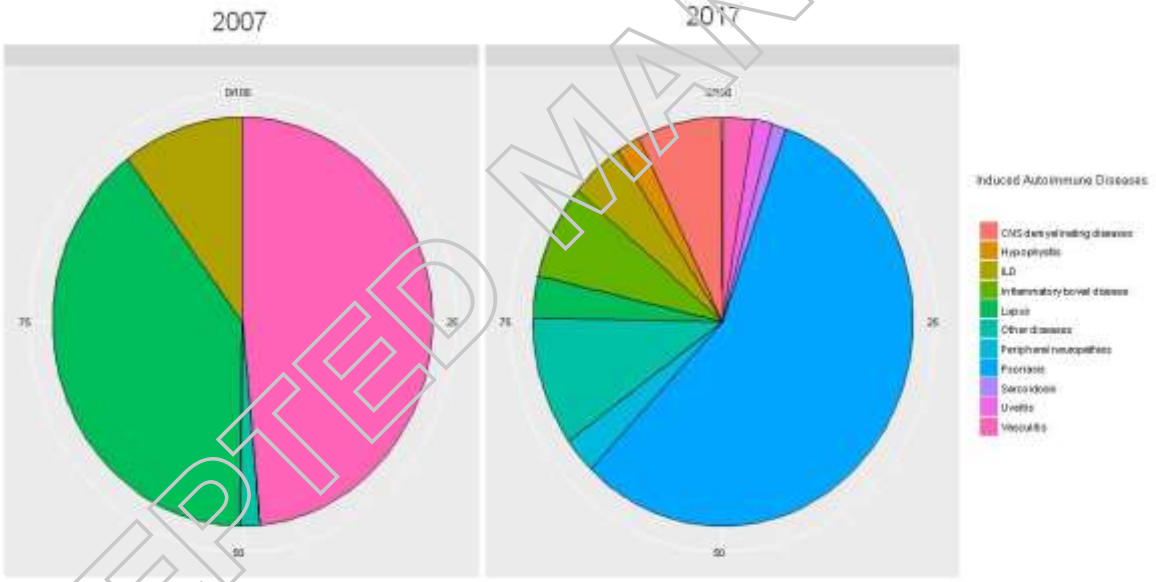
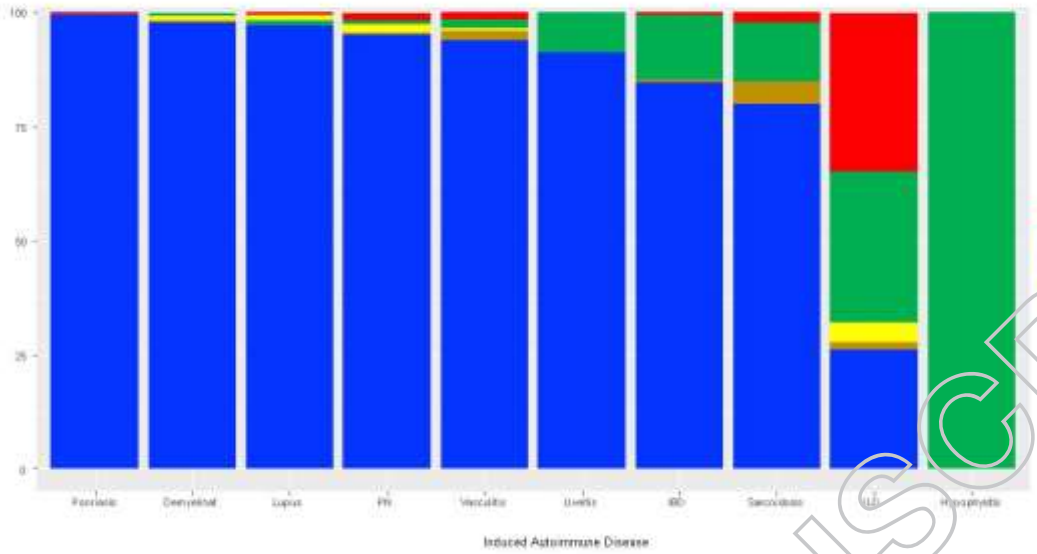


Figure 5. Main groups of biologics involved in the development of induced autoimmune diseases



SUPPLEMENTARY MATERIAL

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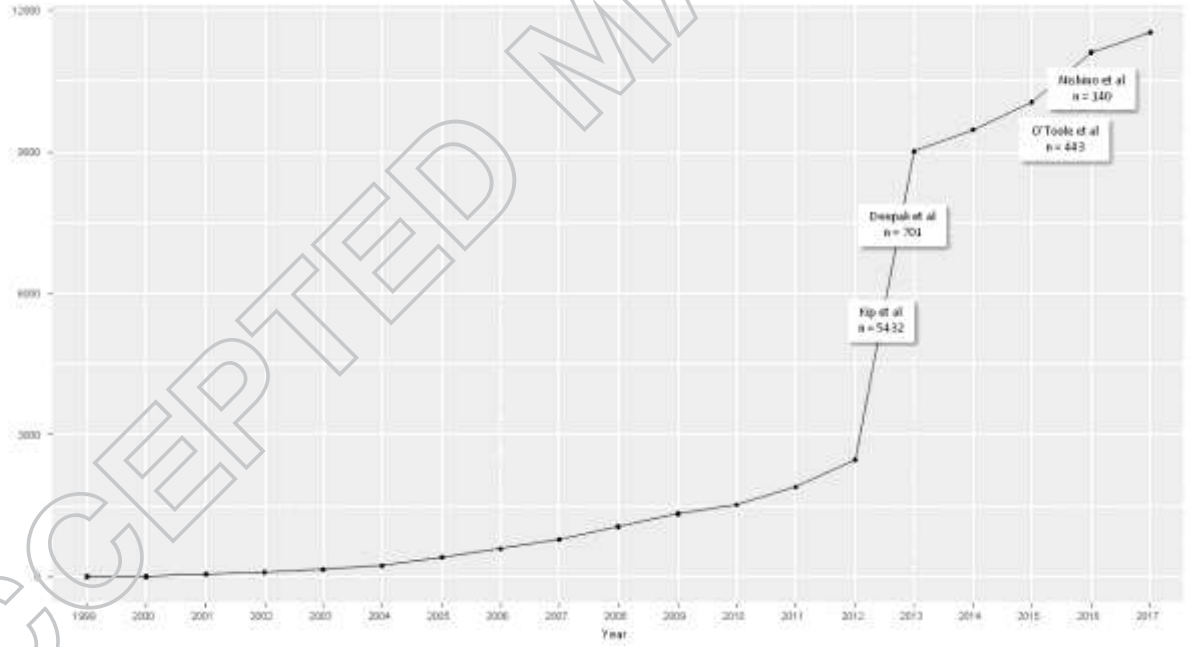

LIST OF ABREVIATIONS

GEAS: Group Study on Autoimmune Diseases
RA: Rheumatoid arthritis
IBD: inflammatory Bowel Disease
SLE: Systemic Lupus Erythematosus
JIA: Juvenile Idiopathic Arthritis
PAN: Polyarteristis Nodosa
PD1: Programmed Death-ligand 1
HLH: Hemophagocytic Lymphohistiocytosis
APS: Antiphospholipid Syndrome
PMR: Polymyalgia Rheumatica
CNS: Central Nervous System
MS: Multiple Sclerosis
NMO: Neuromyelitis Optica
FAERS: Food and Drug Administration Adverse Event Reporting System
ILD: Interstitial Lung Disease
NINE: Nonspecific Interstitial Pneumonia
RCTs: Randomize Control Trials
GN: Glomerulonephritis
ATIN: Acute Tubulointerstitial Nephritis

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