Fortrea

Phase I trials in autoimmune diseases review

Abstract

The main aim of Phase I Clinical Trials is to establish initial safety and dosing. Patients taking part may benefit from the investigational agent, but many won't. Phase I studies are seen as an important step in the evaluation of novel compounds in rheumatology. Such studies must include a potentially active treatment and must not be performed to only evaluate toxicity. Relevant research objectives can be identified, the best phase I study design should be selected, and laboratory tests and biomarkers should be selected for an initial evaluation of pharmacologic activity.

Keywords: *Phase I, autoimmune diseases, clinical trials, biomarkers*

Contributors

Andrea Paula Buschiazzo, MD, Senior Medical Director Fortrea, Argentina.
CABA Board Certified Rheumatologist, Specialist in Clinical Pharmacology

Introduction

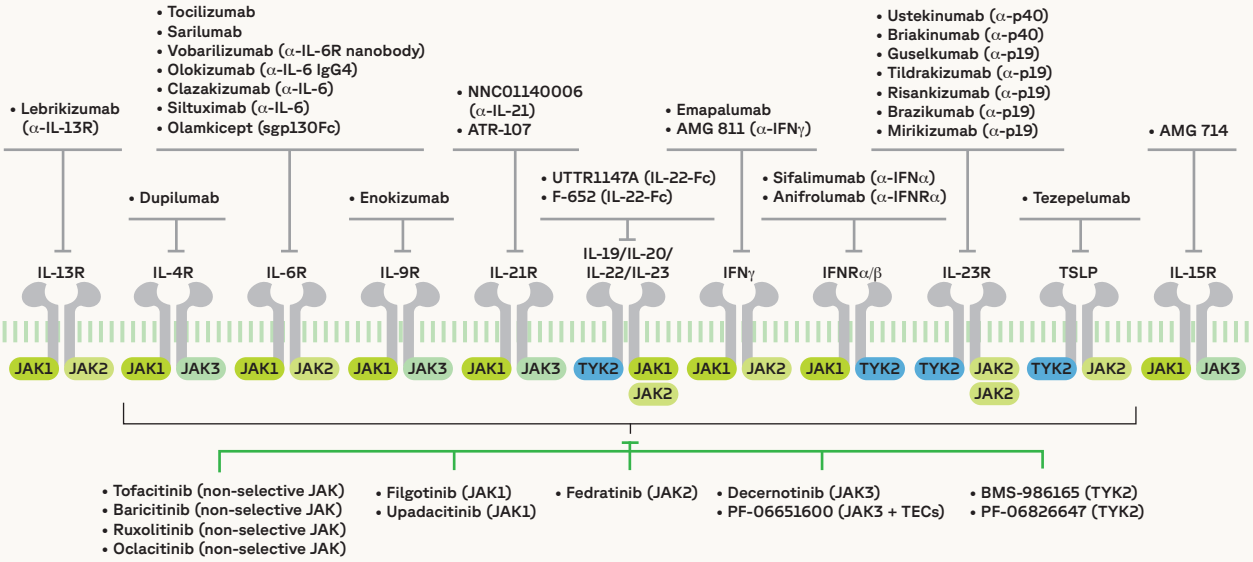
Autoimmune diseases are characterized by dysregulated inflammation against autoantigens and affect 3%–10% of the general population.[1] In the past few decades, biological drugs and small molecule inhibitors targeting inflammatory cytokines, immune cells, and intracellular kinases have revolutionized the treatment of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, ankylosing spondylitis, vasculitis and psoriasis. However, there are still unmet medical needs in terms of efficacy and safety.

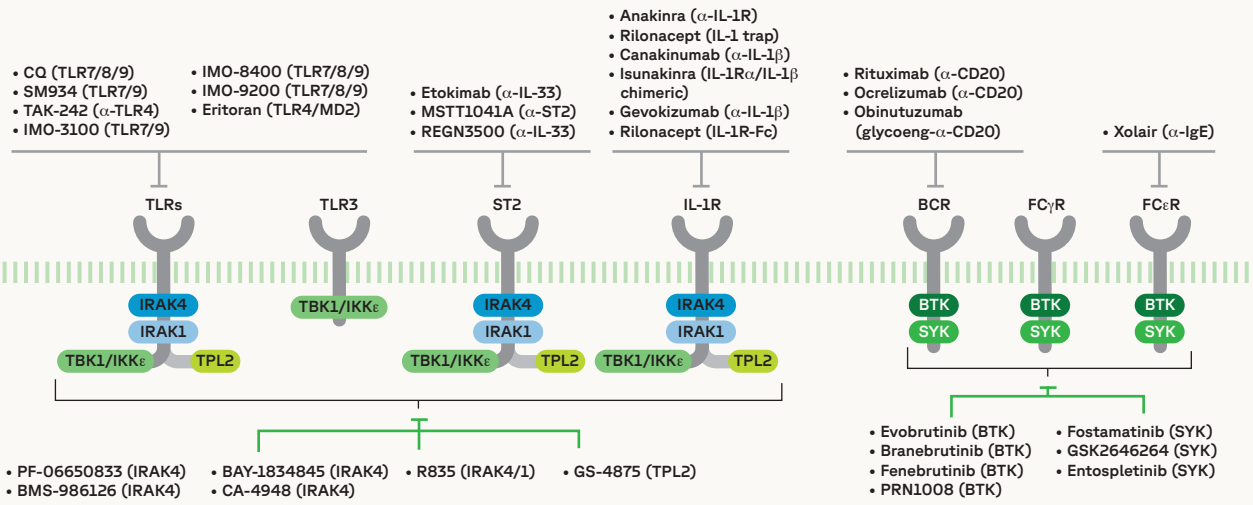
The primary objective of Phase I Clinical Trials is to determine the safety, tolerability and pharmacokinetics (PK) of a compound. Trials have historically been conducted in the logical sequence of single ascending dose, multiple ascending doses, examination of preliminary effect of food on exposure, and potential drug-drug interactions, with assessments to determine the effect of gender, age, bioavailability, and bioequivalence performed as necessary.[2] For autoimmune diseases, dose escalation typically occurs in 20%-30% increments in successive cohorts and there is generally no intrasubject dose escalation.

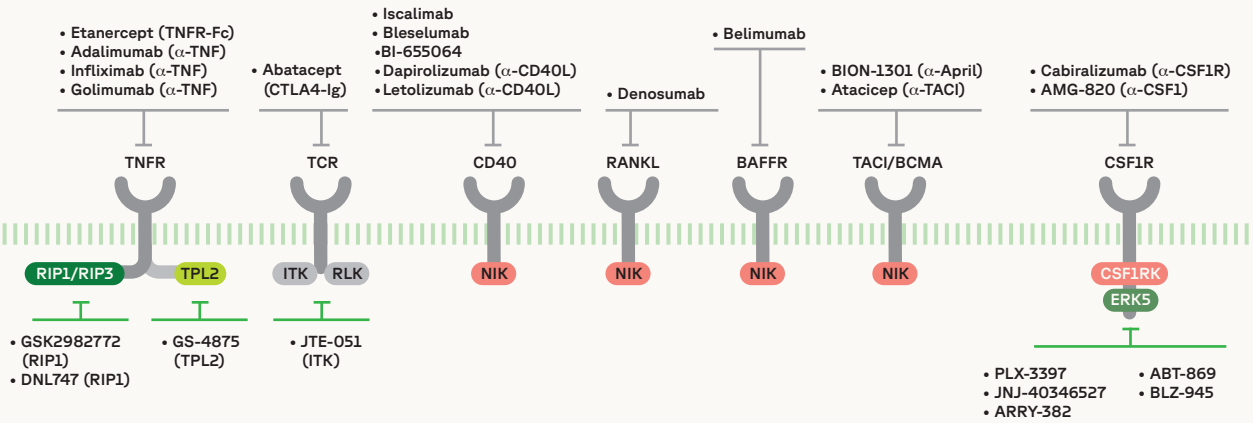
As knowledge about the pathogenesis of disease is rapidly increasing, numerous biological drugs targeting inflammatory signaling pathways are being developed to treat intractable inflammatory diseases.

Biologics (such as antibody antagonists or fusion proteins) have validated several pathogenic pathways involved in these diseases (see Figure 1).[3]

Figure 1: Current landscape of major druggable inflammatory receptors and corresponding kinases implicated in human disease







All small-molecule kinase inhibitors have been evaluated in phase I and beyond. BAFFR, B cell activating-factor receptor; BCMA, B cell maturation antigen; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; CD40L, CD40 ligand; CSF1R, colony-stimulating factor 1 receptor; CTLA4, cytotoxic T lymphocyte-associated protein 4; FcεR, Fcε receptor; IKKε, inhibitor of NF-κB subunit-ε; IL-1R, IL-1 receptor; IRAK, IL-1R-associated kinase; ITK, IL-2-inducible T cell kinase; JAK, Janus-associated kinase; MD2, myeloid differentiation factor 2; NF-κB, nuclear factor-κ-light-chain-enhancer of activated B cells; NIK, NF-κB-inducing kinase; RANKL, receptor activator of NF-κB ligand; RIP1, receptor-interacting protein 1; RLK, resting lymphocyte kinase; ST2, IL-1R-like 1; SYK, spleen tyrosine kinase; TACI, transmembrane activator and CAML interactor; TBK1, TANK-binding kinase 1; TCR, T cell receptor; TEC, Tec protein tyrosine kinase; TLR, Toll-like receptor; TNF, tumor necrosis factor; TNFR, TNF receptor; TPL2, tumor progression locus 2; TSLP, thymic stromal lymphopoietin; TYK2, tyrosine kinase 2.

Phase I trials in autoimmune diseases

Monoclonal antibodies (mAbs) targeting immune checkpoint molecules are revolutionizing rheumatology, not only regarding autoimmune diseases therapeutics and clinical care, but also from a drug development point of view.

Dose of mAbs is not linearly associated with efficacy and toxicity, as opposed to cytotoxic drugs.[4] Patient eligibility criteria might be revisited as the toxicity profile and mechanism of immune-related adverse events are mostly known. The most challenging aspect is understanding the complex PK and pharmacodynamics (PD) characteristics as well as defining which biomarkers to use in patient selection for trial participation. Finally, the early focus on efficacy (and not only dose confirmation) in ascending dose cohorts challenges the traditional phase I/II/III drug development process.

From a cost perspective the design of a phase I study can be positively influenced with proper planning, intelligent study design, and well thought out standardization of design and statistical programming. With protocols that are written flexibly, many objectives can be addressed under one protocol (often with many parts) which can improve the efficiency of the drug development process and decrease the time to Phase II.

Rheumatology clinical trials have advanced to include a rapid dose-escalation phase and large cohorts of patients to demonstrate proof-of-concept and provide strong data as early as phase I. Based on the results of large phase I expansion cohorts, phase II and III models are developed dramatically reducing the drug development time to less than the usual 10 years to 6 years between the first-in-human administration and the drug registration. Results from such cohorts should be used to best prepare later large randomized clinical trials to get drug approval.

Immune-targeted therapies have demonstrated that 'fixed' (pre-treatment) and 'dynamic' (after starting treatment) biomarkers should be distinguished. Biomarkers can be used in many fields of clinical practice and research such as disease diagnosis, disease activity evaluation and disease pathogenesis.

As an example, Systemic Lupus Erythematosus (SLE) is one of the classic autoimmune diseases characterized by a wide variety of autoantibodies. It was found that CXCL13 was overexpressed in SLE patients especially in those with lupus nephritis (LN), which promoted the proliferation of human renal mesangial cells, and inhibition of CXCL13 is a putative new therapeutic target in LN. Serum CXCL13 levels are positively correlated with the SLE Disease Activity Index (SLEDAI), anti-double-stranded DNA (anti-dsDNA) antibody titers, and the prevalence of inflammatory arthritis, while it is inversely correlated with serum levels of complement factors C3 and C4. CXCL13 is also a potential disease activity marker to identify active SLE from inactive SLE, and to identify SLE patients with LN from SLE patients without LN.[5]

Clear guidance is needed in the development and implementation of laboratory biomarkers in autoimmune diseases for clinical trials. Some questions arise about which biomarkers are recommended in a rheumatology trial to find accurate and meaningful information.

Considering that 75% of all medical decisions are somehow affected by laboratory test results, we can estimate the potential harm associated with inadequately validated biomarkers.[6]

Health Verity - Fortrea: phase I trial patient selection in autoimmune disease—systemic lupus erythematosus dataset

[Health Verity integrates patient longitudinal real-world data (RWD) maximizing the investment in clinical trials. It is the only patient journey software solution that can synchronize patients across de-identified, identifiable and investigator data].

Goal: To analyze claims data of lupus patients between June 2019 – June 2022 to monitor diagnosis, treatment and disease management using data delivered by Health Verity.

Cohort Description: Most Frequent Diagnoses / Most Frequent Medications / Most Frequent Lab Tests

Most frequent diagnoses present in claims	# Patients (% of total)
M32.9 (Systemic lupus erythematosus, unspecified)	62,978 (92.9%)
Z79.899 (Other long term {current} drug therapy)	55,331 (81.6%)
I10 (Essential {primary} hypertension)	41,335 (61%)
E55.9 (Vitamin D deficiency, unspecified)	39,987 (59%)
Z23 (Encounter for immunization)	39,145 (57.7%)
Z00.00 (Encounter for general adult medical exam without abnormal findings)	36,387 (53.7%)
Z20.828 (Contact with & exposure to other viral communicable diseases)	31,860 (47%)
Z12.31 (Encounter for screening mammogram for malignant neoplasm of breast)	31,510 (46.5%)
R53.83 (Other fatigue)	30,250 (44.6%)
K21.9 (Gastro-esophageal reflux disease without esophagitis)	30,200 (44.5%)

Most frequent medications present in claims	# Patients (% of total)
NDC: 43598072101 (Hydroxychloroquine Sulfate, tablet)	12,739 (18.8%)
NDC: 68382009601 (Hydroxychloroquine Sulfate, filmed coat tablet)	11,839 (17.5%)
NDC: 66993005702 (Hydroxychloroquine Sulfate, tablet)	10,244 (15.1%)
NDC: 69452015120 (Ergocalciferol, liquid filled capsule)	9,341 (13.8%)
NDC: 66993001968 (Albuterol Sulfate, respiratory aerosol)	8,868 (13.1%)
NDC: 0054327099 (Fluticasone Propionate, nasal spray)	8,827 (13%)
NDC: 65862042005 (Sulfamethoxazole and Trimethoprim, oral tablet)	8,163 (12%)
NDC: 00093317431 (Albuterol Sulfate aerosol, metered)	7,660 (11.3%)
NDC: 59746000103 (Methylprednisolone, oral tablet)	7,286 (10.7%)
NDC: 68180012202 (Cephalexin, oral capsule)	6,945 (10.2%)

Most frequent lab tests present in claims	# Patients (% of total)
CBC with differential	61,813 (81.3%)
Comprehensive metabolic panel (14)	61,632 (81.1%)
Sedimentation rate-Westergren	53,526 (70.4%)
C-Reactive protein, Quant	50,572 (66.5%)
Anti-DNA (DS) AB. QN	47,270 (62.2%)
Vitamin D, 25-hydroxy	45,954 (60.5%)
TSH	43,623 (57.4%)
Lipid panel	40,473 (53.3%)
Complement C3, serum	39,679 (52.2%)
Complement C4, serum	39,523 (52%)

To better analyze the cohort, patient profiles are currently being built to establish presence of comorbidities, treatments, disease monitoring, etc.

- Inclusion of below criteria
- Extract/Transform/Load (ETL) of current data to join all existing tables within the database to create a one-line "snapshot" of a patient for summary statistics and further study

Diagnosis

- Fever
- Non-scarring alopecia
- Oral ulcers
- Subacute cutaneous/ discoid lupus
- Acute cutaneous lupus
- Synovitis
- Delirium
- Psychosis
- Seizure
- Pleural/pericardial effusion
- Acute pericarditis
- Leukopenia
- Thrombocytopenia
- Autoimmune hemolysis
- Proteinuria

Comorbidities

- Hypertension
- Dyslipidemia
- CKD
- CKD-related vascular effects
- Cardiovascular disease
- Nephrotic syndrome

Treatments

- Monoclonal Ab
  - Belimumab
  - Anifrolumab
  - Rituximab
- DMARDS / Immunosuppressives
  - Azathioprine
  - Mycophenolate motefil
  - Cyclosporine
  - Methotrexate
  - Leflunomide
  - Cyclophosphamide

Treatment-related events

- Pneumonia
- Herpes
- Latent tuberculosis
- Hypertension
- Dyslipidemia
- Accelerated artherogenosis
- Cardiovascular disease

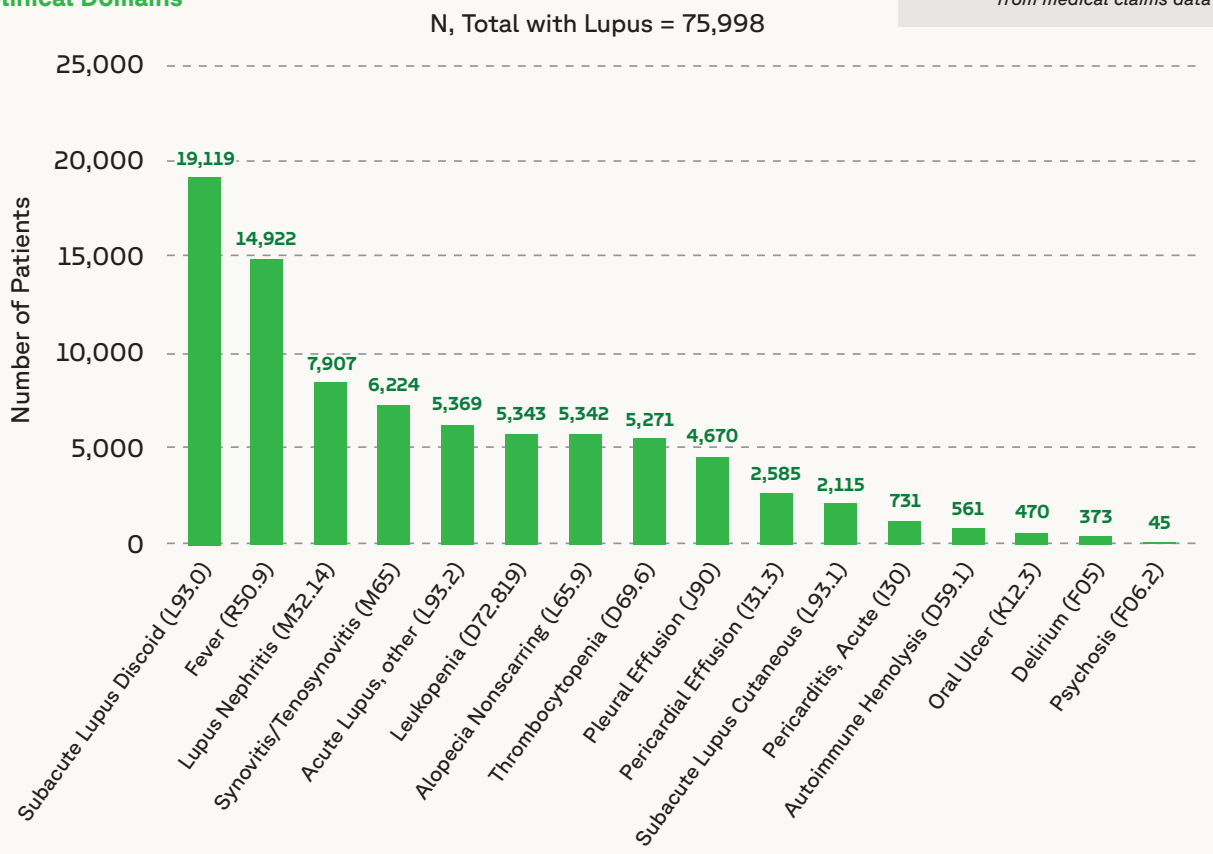
Testing

- Antiphospholipid Ab
- C3/C4
- Anti-dsDNA Ab
- Anti-Smith Ab
- Lupus anticoagulant
- Anticardiolipin Ab
- Anti-B2 glycoprotein I Ab

Lupus patient profile:

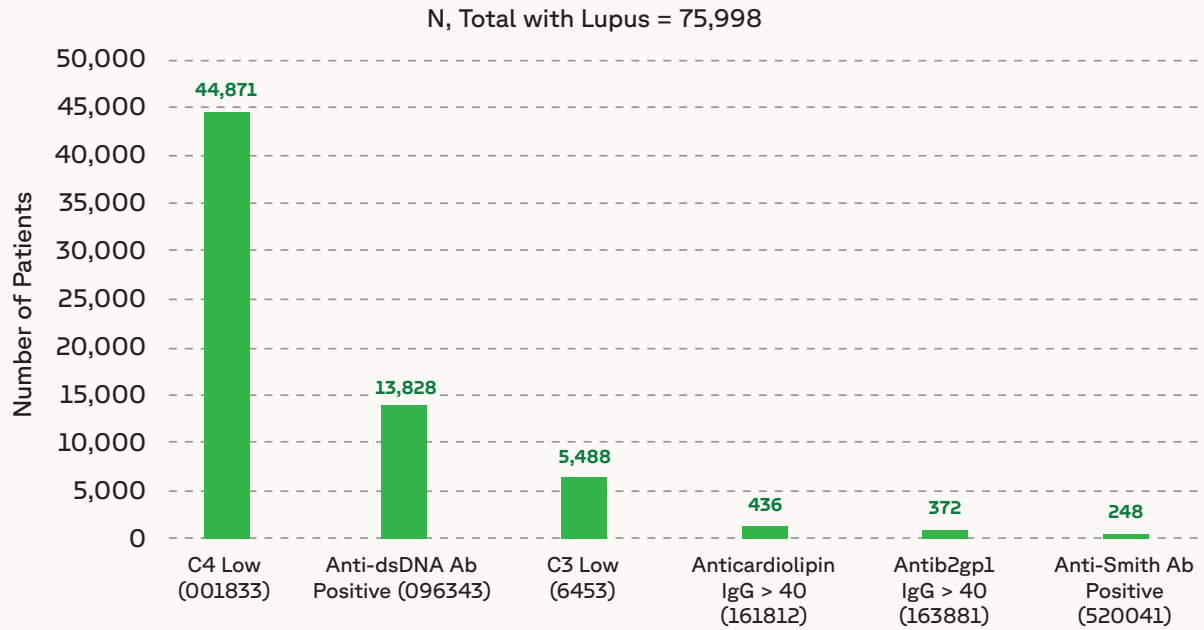
Clinical Domains*

**Identified through ICD-10 search from medical claims data*



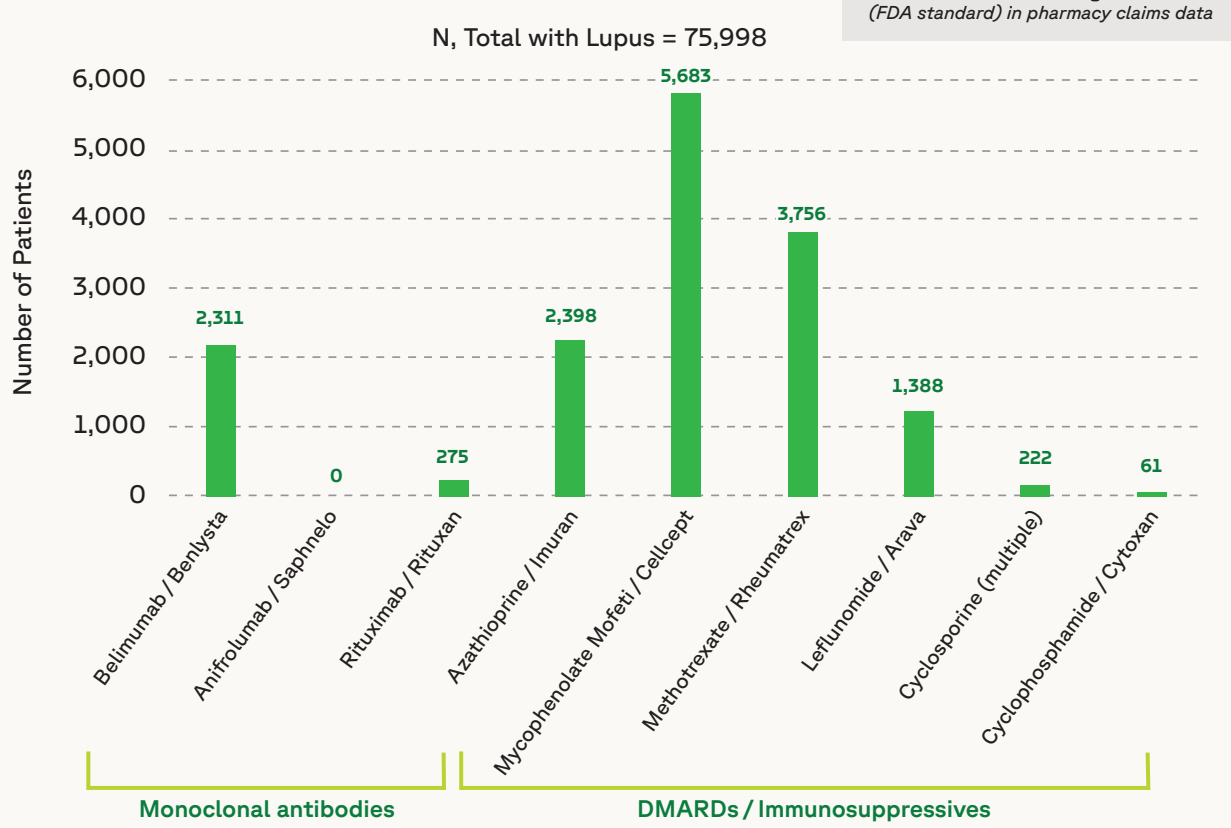
Immunologic Domains*

**Identified through LCA test number or LOINC code from lab test claims data*



Treatments*

**Identified through NDC codes (FDA standard) in pharmacy claims data*



The points to be considered after obtaining the above information are:

- Continue to identify further codes necessary to build and match protocol needs
  - Further filtering of inclusion/exclusion criteria to obtain a more homogeneous study population
- Identify further testing and outcomes available for analysis
- Proof-of-concept (PoC) studies are typically early-stage clinical trials conducted to understand whether an investigational product elicits a pathophysiologic signal, that is, does it produce the expected response in individuals
  - Proved concept of building cohorts based on past claims data
  - Can be used for future clinical trial recruitment
- Limitations
  - Data is severely limited by timeline (2019-2022)—lupus diagnoses usually take years
  - Claims data is powerful, but not very robust—only about ~10% of columns provided contain data
  - Time & effort to translate coding
  - Particularly medications—only NDC code provided and need to translate these into medication, dosage, etc.
- Recommendation
  - Data is good for 'feasibility' checks for clinical trial recruitment, but not necessarily an ideal patient identifier

**Acknowledgment to Health Verity for the support in working with Fortrea obtaining all the Claims lupus data*

Conclusion

To achieve more specific and personalized treatment of patients with autoimmune diseases will require a more detailed understanding of the complexity of individual autoimmune diseases and how they unfold in individual patients. Heterogeneous datasets should be leveraged through development of novel statistical methods to support development of new drugs that are more specific and have fewer side effects but could also be used to develop biomarkers. In combination, these approaches should improve treatment decisions so that the right treatment is given to the right patient at the right time.[6]

Autoimmune diseases are a result of the immune system being misdirected toward its host and have major and increasing unmet clinical needs. In general, present therapies are broadly acting and non-disease specific; consequently, they are associated with numerous side effects. Precise and early intervention strategies are urgently needed.[7]

In contemporary phase I trials, which often include drugs developed with a deep understanding of biology and with the use of biomarkers to select patients, one of the most important objectives involves finding therapeutic signals. Response signals can be better identified if more patients are treated in early-phase trials.[8] Early-phase trials with greater numbers of patients are also able to better identify the spectrum of clinically relevant toxicities.

Expansion cohorts, moving directly from phase I to phase II (and theoretically to phase III), expedite drug development. Newer biomarker-based clinical trials in autoimmune diseases have been associated with improved rates of response, compared to clinical trials that did not use a biomarker to select patients.

New types of early trial design and the availability of datapoints for clinical trials in a way that is verifiable and moves the field forward in a rapid and productive way for patients afflicted with autoimmune diseases is still under development.

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