Highlights

- We analyzed systematically shared drugs and pathways in development between 10 autoimmune and inflammatory diseases (AIDs).
- The 2 AID clusters sharing the highest number of targeted therapies were RA and SLE as well as RA, SpA, psoriasis, and IBD.
- The most common targeted pathways were (by decreasing frequency): JAK-STAT pathways, Th17 axis, TNF-α, IL-6, costimulation molecules, BAFF, CD20, BTK, chemokines and integrins, IL-1, and type I interferon.

Abstract

Background: Pathogenic inflammatory pathways are largely shared between different autoimmune and inflammatory diseases (AIDs). This offers the potential to develop a given targeted therapy in several AIDs.

Methods: We analyzed two clinical trials registries (ClinicalTrials.gov and EU Clinical Trials Register) to identify the targeted therapies whose development is shared between at least two of the most common AIDs [rheumatoid arthritis (RA), spondyloarthritis (SpA), cutaneous psoriasis (cPso), inflammatory bowel diseases (IBD), systemic lupus erythematosus (SLE), primary Sjögren’s syndrome (pSS), systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), giant cell arteritis (GCA), and multiple sclerosis (MS)] using an in-depth repurposing analysis.

Results: We identified 142 shared targeted therapies. The four diseases in which shared targeted therapies were the most numerous were RA (n = 92), cPso (n = 67), IBD (n = 58), and SLE (n = 56). The two clusters of diseases between which the overlap of targeted therapies was the most important were RA and SLE as well as RA, SpA, cPso, and IBD. The targeted therapies which were shared by five diseases or more were abatacept, ustekinumab, rituximab, anakinra, etanercept, infliximab, secukinumab, tocilizumab, tocilizumab, apremilast, baricitinib, belimumab, brodalumab, filgotinib, and upadacitinib. The most frequently targeted molecules and pathways were (by descending frequency): JAK-STAT pathways, Th17 axis, TNF-α, IL-6, costimulation molecules, BAFF, CD20, BTK, chemokines and integrins, IL-1, and type I interferon.

Conclusion: Many targeted therapies are developed in several AIDs, reflecting the overlap of pathogenic pathways and potential of drug repurposing. This suggests that a revision of the current, clinically based classification of AIDs towards a more mechanistic-based taxonomy might be relevant.

Keywords: autoimmune diseases, biological products, drug repositioning, investigational, molecular targeted therapy, therapies

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Introduction
Pharmacological treatment of inflammatory diseases consists mainly of targeting the dysregulated immune system. For decades, this was achieved through the use of glucocorticoids and conventional immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil. The efficacy of these drugs should be balanced against their potential toxicity, with both the former and the latter being related to their generally pleiotropic action.

Recent decades have seen the advent of targeted therapies that have greatly improved the prognosis of inflammatory diseases. More targeted action theoretically allows reduced toxicity without precluding significant efficacy. The emergence of targeted therapies has been enabled by the considerable progress in the understanding of the pathogenesis of inflammatory diseases. The discovery that inflammatory pathways are frequently shared between autoimmune diseases, as highlighted by the efficacy of tumour necrosis factor alpha (TNF-α) inhibitors in the treatment of rheumatoid arthritis (RA), psoriasis or inflammatory bowel diseases (IBD), enables the practice of drug repurposing (or repositioning), which refers to the use in a disease of a drug that has already been approved for use in another disease. This may also lead to a redefinition of inflammatory diseases according to molecular pathways instead of more traditional clinical features.

In this study, we identified in a systematic manner all targeted therapies for which development is shared by at least two diseases among the most common autoimmune and inflammatory diseases (AIDs). We aimed to analyze the concept of drug repurposing and to give an overview of the main molecular pathways targeted in the field of inflammatory diseases. We also sought to isolate clusters of diseases according to molecular and cellular targeted pathways. This may give an insight into advanced repurposing strategies and a future mechanistic-based nosology.

Methods
Selection of auto-immune and inflammatory diseases
The following 10 AIDs were included in the review: RA, spondyloarthritis (SpA) (including non-radiographic axial spondyloarthritis, radiographic axial spondyloarthritis, peripheral spondyloarthritis, psoriatic arthritis), cutaneous psoriasis (cPso), IBD (including Crohn’s disease and ulcerative colitis), systemic lupus erythematosus (SLE), primary Sjögren’s syndrome (pSS), systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), giant cell arteritis (GCA) (also including Takayasu arteritis and polymyalgia rheumatica) and multiple sclerosis (MS). The chosen diseases were selected because of their significance regarding their epidemiology and burden on public health, and because there is a strong interest in the development of targeted therapies for those diseases.

Extraction of trials and molecules
For each of these diseases, we selected all clinical trials registered with the two most important clinical trials registries (ClinicalTrials.gov and EU Clinical Trials Register). Duplicates between the two registries were excluded. The search was performed up to 5 October 2019. Using R statistical software, we identified all molecules studied in at least 2 of the 10 predefined diseases. From this list, we retained all targeted therapies, defined as drugs specifically designed to block specific molecules, receptors, or pathways involved in the development of autoimmune diseases. We excluded from this analysis all non-pharmacological interventions, and all pharmacological agents leading to a non-specific blockade of the immune system, such as classical immunosuppressive agents. We considered only the originators of biological disease-modifying anti-rheumatic drugs and excluded biosimilars. Targeted therapies were classified according to their mechanisms of action. For each identified molecule, the most advanced and latest known stage of drug development in each disease was extracted from the registries. The number of targeted therapies shared by a disease with each of the other diseases was calculated.

Statistics
Quantitative variables were described using numbers and percentages. All interventions studied in at least two of the diseases were identified using R statistical software version 3.6.1, package XLConnect version 0.2–15. Venn diagrams represented in Figure 1 were computed using R software package “VennDiagram” version 1.6.20. The overlaps between molecules (Figure 2) were computed using the R software package “UpSetR” version 1.4.0.
Figure 1. Associations of diseases based on the number of shared targeted therapies. For each disease, a Venn diagram shows three closely related diseases based on the number of shared targeted therapies. (A) For RA (also valid for SLE). (B) For SpA (also valid for cPso and IBD). (C) For pSS. (D) For SSc. (E) For IIM. (F) For GCA. (G) For MS. Numbers in parentheses represent the number of trials.

cPso, cutaneous psoriasis; GCA, giant cell arteritis; IBD, inflammatory bowel diseases; IIM, idiopathic inflammatory myopathies; MS, multiple sclerosis; pSS, primary Sjögren’s syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis.
Data statement
Data that support the findings of this study are available from the authors upon request.

Results
Our systematic review identified 142 targeted therapies assessed in at least 2 of the 10 predefined AIDs.

Table 1 shows, for each disease, the number of clinical trials extracted from the two registries and the number of targeted therapies shared with other diseases.

Shared targeted therapies identified for inflammatory diseases
Rheumatoid arthritis. From a total of 1851 clinical trials in rheumatoid arthritis, we identified 92 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with RA were: SLE (n = 41 molecules), IBD (n = 35), and cPso (n = 33) (Figure 1A).

Spondyloarthritis. We identified 534 trials conducted in spondyloarthritis. From these trials, we found 36 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with SpA were: cPso (n = 26), RA (n = 26), and IBD (n = 21) (Figure 1B).

Cutaneous psoriasis. From a total of 1267 trials in cPso, we identified 67 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with cPso were: IBD (n = 33), RA (n = 33), and SpA (n = 26) (Figure 1B).

Inflammatory bowel diseases. We identified 1748 trials in IBD. From these trials, we found 58 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with IBD were: RA (n = 35), cPso (n = 33), and SpA (n = 21) (Figure 1B).

Systemic lupus erythematosus. From 520 clinical trials in SLE, we identified 56 targeted therapies...
shared with at least another disease. The three diseases sharing the highest number of molecules under development with SLE were: RA \((n=41)\), cPso \((n=17)\), and IBD \((n=16)\) (Figure 1A).

**Primary Sjögren’s syndrome.** From 140 clinical trials in pSS, we found 22 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with pSS were: RA \((n=16)\), SLE \((n=14)\), and IIM \((n=7)\) (Figure 1C).

**Systemic sclerosis.** We identified 333 trials conducted in SSc. From these trials, we found 18 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with SSc were: RA \((n=10)\), SLE \((n=10)\), and IIM \((n=7)\) (Figure 1D).

**Idiopathic inflammatory myopathies.** From 115 trials in IIM, we identified 20 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with IIM were: SLE \((n=13)\), RA \((n=12)\), and cPso \((n=9)\) (Figure 1E).

**Giant cell arteritis, Takayasu arteritis, and polymyalgia rheumatica.** We identified 87 trials conducted in GCA. From these trials, we found 15 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with GCA were: RA \((n=14)\), SpA \((n=10)\), and SLE \((n=9)\) (Figure 1F).

**Multiple sclerosis.** We identified 1673 clinical trials in MS. From these trials, we found 28 targeted therapies shared with at least another disease. The three diseases sharing the highest number of molecules under development with MS were: RA \((n=18)\), SLE \((n=13)\), and IBD \((n=12)\) (Figure 1G).

The complete list of the 142 shared targeted therapies and the diseases in which they are developed, as well as their mechanism of action, is shown in the Supplemental Table S1.

### Table 1. Trials identified and number of shared targeted therapies for each disease.

| Diseases                                | Identification of trials | Number of shared targeted therapies* |
|-----------------------------------------|--------------------------|-------------------------------------|
|                                         | From ClinicalTrials.gov  | From EU-CTR | Duplicates | Total number of trials |                                      |
| Rheumatoid arthritis                    | 1642                     | 554         | 345        | 1851                  | 92                                   |
| Spondyloarthritis                       | 453                      | 182         | 101        | 534                   | 36                                   |
| Cutaneous psoriasis                     | 1070                     | 390         | 193        | 1267                  | 67                                   |
| Inflammatory bowel diseases             | 1369                     | 592         | 213        | 1748                  | 58                                   |
| Systemic lupus erythematosus            | 456                      | 126         | 62         | 520                   | 56                                   |
| Sjögren’s syndrome                      | 125                      | 31          | 16         | 140                   | 22                                   |
| Systemic Sclerosis                      | 284                      | 63          | 14         | 333                   | 18                                   |
| Idiopathic inflammatory myopathies      | 105                      | 21          | 11         | 115                   | 20                                   |
| Giant cell arteritis                    | 71                       | 26          | 10         | 87                    | 15                                   |
| Multiple sclerosis                      | 1480                     | 412         | 219        | 1673                  | 28                                   |

*With other diseases from the table.

Inflammatory diseases sharing the highest number of targeted therapies

The number of targeted therapies shared by the different sets of diseases is shown in Figure 2. Among the targeted therapies shared by only 2 of the ten diseases, 12 are shared between RA and SLE, 11 between RA and cPso, 10 between cPso and IBD, 10 between RA and IBD, 5 between SpA and cPso, and 4 between RA and MS.
Among the targeted therapies shared by three diseases, four are shared between RA, SLE, and pSS, four between RA, SLE, and MS, and three between RA, cPso, and IBD. Among the targeted therapies shared by four diseases, four are shared between RA, SpA, cPso, and IBD and two are shared between SpA, cPso, IBD, and SLE.

Most commonly shared targeted therapies for inflammatory diseases

We identified one targeted therapy investigated in all 10 diseases: abatacept, a fusion protein consisting of CTLA4 and an immunoglobulin chain. Two targeted therapies were assessed in 8 of the 10 diseases: ustekinumab [anti-interleukin (IL)-12/IL-23 p40 subunit monoclonal antibody] and rituximab (anti-CD20 monoclonal antibody). The eight diseases in which ustekinumab was studied are: RA, SpA, cPso, IBD, SLE, IIM, GCA, and MS. The eight diseases in which rituximab was assessed are: RA, SpA, IBD, SLE, pSS, SSc, IIM, and MS. Five targeted therapies was evaluated in 7 of the 10 diseases: anakinra, etanercept (and its biosimilars), infliximab (and its biosimilars), secukinumab, tofacitinib. Anakinra is an IL-1 receptor antagonist investigated in RA, cPso, SLE, pSS, IIM, GCA, and MS. Etanercept is a TNF-α inhibitor tested in RA, SpA, cPso, SLE, pSS, IIM, and GCA. Infliximab, another TNF-α inhibitor, was assessed in RA, SpA, cPso, IBD, SLE, IIM, and GCA. Secukinumab is an anti-IL-17 monoclonal antibody evaluated in RA, SpA, cPso, IBD, SLE, GCA, and MS. Tofacitinib is a selective Janus kinase (JAK)1 and JAK3 inhibitor investigated in RA, SpA, cPso, IBD, SLE, pSS, SSc, IIM, and GCA. We identified two targeted therapies assessed in 6 of the 10 diseases: alemtuzumab and tocilizumab. Alemtuzumab is an anti-CD52 monoclonal antibody; it was studied in RA, IBD, SLE, SSc, IIM, and MS. Tocilizumab is an anti-IL-6R monoclonal antibody assessed in RA, SpA, pSS, SSc, IIM, and GCA. Seven targeted therapies were studied in 5 of the 10 diseases. Adalimumab (and its biosimilars), apremilast, baricitinib, belimumab, brodalumab, filgotinib, and upadacitinib. Adalimumab, an anti-TNF-α monoclonal antibody, was investigated in RA, SpA, cPso, IBD, and GCA. Apremilast, a type 4 phosphodiesterase inhibitor, was evaluated in RA, SpA, cPso, IBD, and IIM. Baricitinib is a selective JAK1 and JAK2 inhibitor tested in RA, SpA, cPso, IBD, and GCA. Belimumab, an anti-B-cell activating factor (BAFF) monoclonal antibody, was assessed in RA, SLE, pSS, SSc, and IIM. Brodalumab is a monoclonal antibody directed against the receptor of IL-17A; it was studied in RA, SpA, cPso, IBD, and SSc. Filgotinib and upadacitinib are selective JAK1 inhibitors both investigated in RA, SpA, IBD, and SLE; filgotinib was also tested in pSS and upadacitinib in GCA.

The latest known development phase and status of the drugs for each of the diseases are shown in Supplemental Table S2.

Most commonly shared molecular pathways targeted in inflammatory diseases

In RA, the pathways most commonly targeted by the shared therapies identified are: Th17 cytokines (through anti-IL-23, anti-IL-22, and anti-IL-17 monoclonal antibodies) (n=9 molecules), TNF-α (n=9), Janus kinase-signal transduction and activation of transcription (JAK-STAT) (n=8), B-cell activating factor (BAFF) (n=7), IL-6 (n=7), Bruton’s tyrosine kinase (BTK) (n=6), CD20 (n=5), costimulation molecules (n=4), integrins or selectins (n=4), chemokines (n=4), granulocyte-macrophage colony-stimulating factor (GM-CSF) (n=3), IL-1 (n=3), and p38 MAPK (n=3). In SpA, the most commonly targeted shared pathways are: Th17 cytokines (n=11), TNF-α (n=7), JAK-STAT (n=6), IL-6 (n=3), integrins or selectins (n=2), and costimulation molecules (n=2). In cPso, the most commonly targeted shared pathways are: Th17 cytokines (n=14), JAK-STAT (n=8), intracellular kinases (excluding JAK kinases) (n=7), TNF-α (n=5), Th1 cytokines (n=5), costimulation molecules (n=4), and integrins or selectins (n=3). In IBD, the most commonly targeted shared pathways are: JAK-STAT (n=9), Th17 cytokines (n=9), TNF-α (n=6), chemokines (n=3), IL-6 (n=3), and integrins or selectins (n=2). In SLE, the most commonly targeted shared pathways are: costimulation molecules (n=7), JAK-STAT (n=7), BAFF (n=7), CD20 (n=4), BTK (n=4), type I interferon (IFN) (n=4), IL-6 (n=3), and proteasome (n=2). In pSS, the most commonly targeted shared pathways are: BAFF (n=5), costimulation molecules (n=4), and BTK (n=2). In SSc, the most commonly targeted shared pathways are: JAK-STAT (n=2) and IL-6 (n=2). In IIM, the most commonly targeted shared pathways are: type I IFN (n=4), TNF-α (n=2) and IL-1 (n=2). In GCA, the most commonly targeted shared pathways are: TNF-α (n=3), IL-1 (n=3), IL-6 (n=3),...
Th17 cytokines \((n = 2)\) and JAK-STAT \((n = 2)\). In MS, the most commonly targeted shared pathways are: Th17 cytokines \((n = 3)\), CD20 \((n = 3)\), BAFF \((n = 3)\) and integrins or selectins \((n = 3)\).

**Discussion**

In this systematic review, we identified all targeted therapies for which development is shared among the main AIDs. As the term “development” covers phase IV post-marketing studies, most drugs being used currently in clinical practice also appear among the identified targeted therapies.

We identified 142 targeted therapies shared among the 10 pre-specified diseases. Among them, 92 molecules (65%) were developed for, or used in, RA. This could reflect the interest in the development of treatments for this disease,\(^1\) as well as the existence of pathogenic mechanisms shared with other diseases.\(^2,3\) More than one-third of the shared targeted therapies were studied in cPso, IBD, and SLE, which we attribute similarly to the stake represented by the development of new effective molecules in these diseases and to the existence of shared therapeutic targets.\(^4\) Conversely, very few of the shared targeted therapies were identified in SSc and MS relative to the high number of clinical trials extracted. This is likely due to their particular pathophysiology, SSc involving not only immune system dysfunction but also microvascular changes and fibrosis,\(^4\) and MS being an autoimmune disease affecting a single organ enclosed behind the blood-brain barrier.

On the whole, the pathways most frequently targeted by the shared therapies were (in descending frequency of molecules): JAK-STAT pathways, Th17 axis, TNF-\(\alpha\), IL-6, costimulation molecules, B cells (mainly through BAFF and BTK inhibitors and anti-CD20 antibodies), molecules involved in leukocyte chemotaxis (integrins, selectins and chemokines), IL-1, and type I IFN.

We could isolate two clusters of diseases in which the overlap of targeted therapies was particularly important: (1) RA and SLE; and (2) RA, SpA, cPso, and IBD. It should be kept in mind that diseases in which the number of trials (and thereby of studied molecules) is large obviously tend to share more molecules between them. As a result, one could not simply consider the number of shared molecules as the reflection of pathophysiologic and therapeutic relatedness. Nonetheless, this important overlap reflects similarities in the pathways targeted in these diseases. For instance, JAK-STAT, BAFF, BTK, CD20, and costimulation molecules are targeted by several drugs in development in both RA and SLE.

Targeting JAK-STAT pathways is of interest in these two diseases; for example, the inhibition of JAK1 blocks both IL-6 and type I IFN signalling, two cytokines whose role in the pathophysiology of RA and SLE, respectively, is known.\(^5\) As for the targeting of BAFF, BTK, CD20 and costimulation molecules, it takes advantage of the pathogenic role of B cells and auto-antibodies in RA and SLE.\(^6\) About the cluster formed by RA, SpA, cPso, and IBD, the main pathways that underlie the overlap of targeted therapies were Th17 cytokines, JAK-STAT, and TNF-\(\alpha\). Many studies have indeed provided evidence for the involvement of the Th17 axis in these four diseases.\(^7\) The development of several JAK inhibitors in RA, SpA, cPso, and IBD was expected, considering the number of cytokines involved in their pathogenesis that signal through the JAK-STAT pathways.\(^8\) Finally, the role of TNF-\(\alpha\) in this cluster is today well-documented, both by experimental data and by the clinical success of TNF-\(\alpha\) inhibitors.\(^9\)

Compared with the relatively limited number of clinical trials in pSS and IIM, both diseases shared a proportionally high number of targeted therapies with RA and SLE. The main shared pathways targeted in pSS, RA, and SLE were costimulation molecules and BAFF, reflecting the B cell-mediated nature of Sjögren’s disease, as previously mentioned for RA and SLE.\(^10\) The main pathway targeted in both IIM and SLE was type I IFN. This comes from the fact that dermatomyositis (one of the IIM) and SLE are known type I IFN-mediated diseases,\(^11\) as proven by the frequent existence of an IFN signature and by the efficacy of anti-IFN therapies in patients affected by SLE or dermatomyositis.\(^12\) Between IIM and RA, the most shared targeted pathways were TNF-\(\alpha\) and IL-1.

Among the 15 targeted therapies that GCA shared with others diseases, 14 were shared with RA. These 14 molecules targeted mainly TNF-\(\alpha\), Th17 cytokines, IL-6, IL-1, and JAK-STAT; cytokines and pathways for which a role in RA and GCA pathogenesis has been established.\(^13\)
Many of the drugs used currently to treat AIDs result from repurposing, especially from other autoimmune diseases (e.g., TNF inhibitors, most of which were approved in RA and repurposed a few years later in SpA). Identification of candidates for drug repurposing is classically made possible through hypotheses regarding disease pathogenesis. Besides, repurposing candidates could arise by observation of off-targets effects and through more modern approaches such as, for example, signature matching (which consists of comparing the transcriptomic signature of a molecule with that of another drug already used in a disease) or molecular docking (a structure-based strategy to predict affinity between a drug and a therapeutic target). The mechanistic-based repurposing strategy underlies, probably to a large extent, the overlaps that we identified in this review.

Currently, AIDs are defined mainly on the basis of their clinical characteristics. However, the similarities between different diseases and, conversely, the heterogeneity within a single entity, resulting in the inability to classify some patients should lead to a reclassification of these diseases. Thanks to considerable advances in the comprehension of AIDs pathogenesis and because it might determine the best therapeutic choices, the next classification may distinguish different entities on the basis of the predominant mechanism involved in disease pathogenesis. For example, the role of type I IFN in several rheumatic diseases has led to the emergence of the concept of type-I interferon mediated diseases. At least, currently defined diseases may be further subdivided according to molecular features (for instance, in RA, we would distinguish predominantly B-cell mediated forms, predominantly TNF-mediated forms, and so on). Thus, the above-mentioned shared molecular targets could be seen as potential candidates for such mechanistic-based classifications.

This study has some limitations. The systematic method for screening clinical trials we used in this systematic review did not allow us to determine whether a study had been completed or not, and whether the primary end-point had been reached. Yet, early termination could reflect a lack of involvement of the studied pathway in the pathogenesis of the disease (beside other reasons such as a lack of power of the study, insufficient efficacy or the involvement of the pathway only in subgroups of patients). The most prominent example is the Th17 pathway that we identified as one of the most frequently targeted by drugs developed in RA. However, no anti-Th17 agent is currently approved in this disease because trials of these therapies have failed to reach their primary end-points in later phase studies. Accordingly, identified drugs should not be strictly interpreted as those effective in each disease. Rather, our results reflect repurposing strategies that rely on mechanistic hypotheses but do not guarantee that good results will be obtained in clinical trials. Finally, our results should be interpreted keeping in mind that the decision to test a given molecule in a disease, although largely dependent on supposed pathophysiology, is also conditioned by marketing considerations such as a lack of effective therapies in a disease or the market-share it may represent. Also, older targeted therapies are more likely to have been tested in more indications than newer ones.

In conclusion, this analysis highlighted the numerous overlaps of targeted therapies that exist between AIDs. The limited number of inflammatory pathways involved in the pathogenesis of those diseases enables a high potential for drug repurposing and might explain the identified overlaps. This may also prompt a redefinition of AIDs towards a new nosology based not only upon clinical but also mechanistic features. This might be all the more interesting in the near future, as the identification of the prominent pathophysiology may determine the optimal targeted therapy to be used.

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Arthur PETITDEMANGE: no competing interest.
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Ethics
Ethics approval and informed consent were not required for the present study since it did not involve human participants.

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