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Development of a Comprehensive List of Immunosuppressive Therapies to Enable a Multi-Data Source Global Real-World Effectiveness Program of Immunocompromised Patients

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Why did we perform this research?

- Immunocompromised individuals form a heterogeneous population for which evaluation of the effectiveness and safety of medicines and vaccines is challenging[1–3]
- There is a lack of agreement as to which medications are considered immunosuppressive
- In 2021, AZD7442 (tixagevimab/cilgavimab) received Emergency Use Authorization in the US to prevent COVID-19 in immunocompromised individuals, including those receiving immunosuppressive therapies[4]

Objective: To develop a comprehensive list of immunosuppressive therapies to support global real-world studies in immunocompromised individuals

How did we perform this research?

- A rigorous process was used to develop the comprehensive list of immunosuppressive therapies

Sources for immunosuppressive medications

- NLM Value Set Authority Center
- Master Protocol, COVID-19 Natural History, Sentinel Initiative 2020
- Participants in the AZD7442 real-world evidence program from:
  - US Department of Veterans Affairs
  - University of Pittsburgh Medical Center
- The SUPERNOVA (AZD3152) clinical trial (NCT05648110)[5]

Criteria for acceptance

- Medications on ≥3 source lists were accepted
- Medications on only 1–2 source lists were evaluated for:
  - Relevance to clinical judgement (e.g., use in clinical care, use in the clinical trial)
  - Determination of approved indications and mechanisms of action

Review process

- Medical review by the authors
- Adjudication of the selected immunosuppressive medications by the SUPERNOVA (AZD3152) clinical trial (NCT05648110)[5] investigators

Code assignment per medication included in the final comprehensive list

- NLM RxNorm standard clinical drug vocabulary codes (ingredient level)
- NDC universal product identifiers (11 digits)
- Centers for Medicare & Medicaid Services HCPCS codes
- World Health Organization ATC-5 drug codes

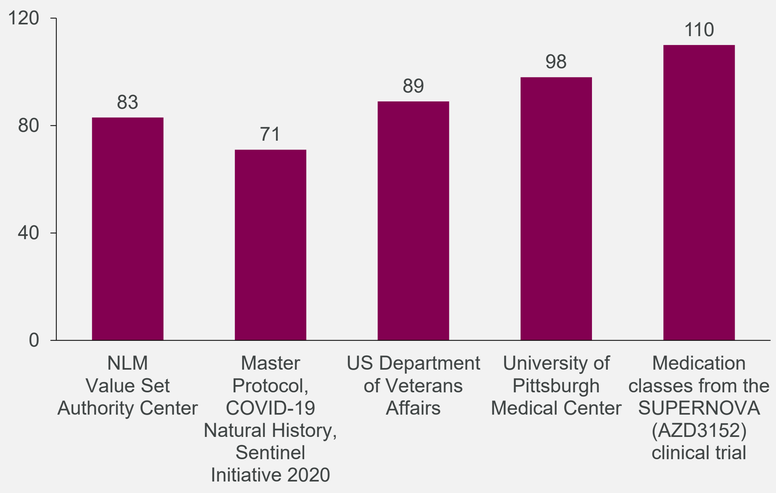
ATC, Anatomical Therapeutic Chemical; HCPCS, Healthcare Common Procedure Coding System; NDC, National Drug Code; NLM, National Library of Medicine.

What did we find?

Development of a comprehensive list of immunosuppressive medications

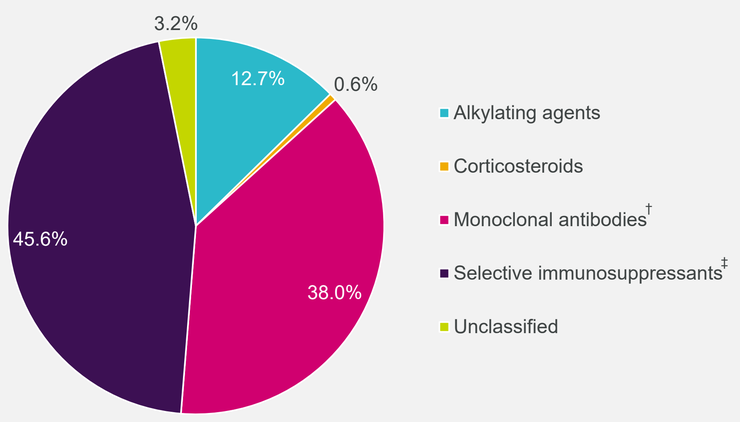
- The five source lists contained 71–110 medications (**Figure 1**)
- The final comprehensive list of medications includes:
  - 157 distinct medications across 21 classes (**Figure 2**)
  - 143 RxNorm codes, 151 Anatomical Therapeutic Chemical-5 codes, 256 Healthcare Common Procedure Coding System codes, 3433 National Drug Code codes and 4 medications without codes that were approved in countries not using the above coding systems (**Figure 3**)
- A sample list of medications, their classifications and their respective codes are provided in **Table 1**

Figure 1. Number of immunosuppressive medications across the five source lists



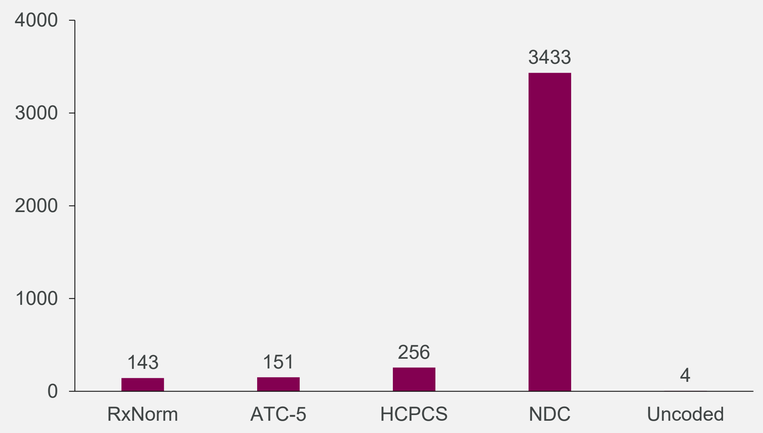
NLM, National Library of Medicine.

Figure 2. Immunosuppressive medications by drug class in the final comprehensive medication list



†Anti-CD20s, anti-interferons, inhibitors of Bruton's tyrosine kinase, interleukin (1, 17, 23 or other) and tumour necrosis factor-alpha, complement inhibitors, integrin receptor agonists, selective T-cell co-stimulation blockers and general monoclonal antibodies.
‡Anti-metabolites, inhibitors of calcineurin, mammalian target of rapamycin and Janus kinase, sphingosine-1-phosphate receptor modulators and general immunosuppressants.

Figure 3. Number of medication codes included in the final comprehensive medication list



ATC, Anatomical Therapeutic Chemical; HCPCS, Healthcare Common Procedure Coding System; NDC, National Drug Code.

Using medication names and the most appropriate set of standard codes maximises the likelihood of finding relevant records among real-world datasets

How do these data inform clinical practice?

This analysis has produced a comprehensive list of immunosuppressive medications with associated codes that can help identify immunocompromised patients

These results can be used as a template to ensure consistency across study cohorts in future clinical trials and in real-world observational studies of immunocompromised individuals

Limitations

- This list of immunosuppressive medications was translated into four code systems commonly used in the US and EU, although this does not cover all possible coded and uncoded ways in which medications may be documented in healthcare/real-world data

Table 1. Sample list of medications, their classifications and respective codes

Generic name	Trade name(s)	Drug category	RxNorm label (code)	ATC label (code)
Monoclonal antibodies				
Abatacept	Orencia	Selective T-cell co-stimulation blocker	Abatacept (614391)	Abatacept (L04AA24)
Acalabrutinib	Calquence	Bruton tyrosine kinase inhibitor	Acalabrutinib (1986808)	Acalabrutinib (L01EL02)
Adalimumab	Humira, Humira Pen, Humira Pen Crohns/UlcerColit/HidraSuppur, Humira Pen Psoriasis/Uveitis Starter Package, Humira Pediatric, Humira Pediatric Crohn's Disease Prefill Syringe Start Pack, Amjevita, Amjevita SureClick, Humira Pre-filled Syringe, Humira Pen Psoriasis/Uveitis/Adol HidraSuppur Starter Pack, Humira Pen Crohns/Ulcer Colitis/Hidradenitis Suppurati StrPk, Humira Pen Psoriasis/Uveitis Starter Pack, Humira Pen Pediatric Ulcerative Colitis Starter Pack	Tumour necrosis factor-alpha inhibitor	Adalimumab (327361)	Adalimumab (L04AB04)
Alemtuzumab	Campath, MabCampath, Lemtrada	General	Alemtuzumab (117055)	Alemtuzumab (L04AA34)
Anakinra	Kineret	Interleukin-1 inhibitor	Anakinra (72435)	Anakinra (L04AC03)
Anifrolumab	Saphnelo	Anti-interferon	Anifrolumab (2565265)	Anifrolumab (L04AA51)
Basiliximab	Simulect	Interleukin inhibitor (other)	Basiliximab (196102)	Basiliximab (L04AC02)
Belatacept	Nulojix	Selective T-cell co-stimulation blocker	Belatacept (1112973)	Belatacept (L04AA28)
Belimumab	Benlysta	General	Belimumab (1092437)	Belimumab (L04AA26)
Benralizumab	Fasenra	Interleukin inhibitor (other)	Benralizumab (1989100)	Benralizumab (R03DX10)
Brodalumab	Siliq	Interleukin-17 inhibitor	Brodalumab (1872251)	Brodalumab (L04AC12)
Canakinumab	Ilaris	Interleukin-1 inhibitor	Canakinumab (853491)	Canakinumab (L04AC08)
Certolizumab pegol	Cimzia	Tumour necrosis factor-alpha inhibitor	Certolizumab pegol (709271)	Certolizumab pegol (L04AB05)
Selective immunosuppressants				
Abrocitinib	Cibinqo	Janus kinase inhibitor	Abrocitinib (2591476)	Abrocitinib (D11AH08)
Alefacept	Amevive	General	Alefacept (299635)	Adalimumab (L04AB04)
Altretamine	Hexalen	General	Altretamine (5296)	Altretamine (L01XX03)
Apremilast	Otezla	General	Apremilast (1492727)	Apremilast (L04AA32)
Azacitidine	Onureg, Vidaza	Anti-metabolites	Azacitidine (1251)	Azacitidine (L01BC07)
Azathioprine	Azasan, Imuran	General	Azathioprine (1256)	Azathioprine (L04AX01)
Baricitinib	Olumiant	Janus kinase inhibitor	Baricitinib (2047232)	Baricitinib (L04AA37)
Belumosudil	Rezurock	General	Belumosudil (2564025)	Belumosudil (L04AA48)
Bleomycin	Blenoxane	Anti-metabolites	Bleomycin (1622)	Bleomycin (L01DC01)
Bortezomib	Velcade, Chemobort, Bortecad	General	Bortezomib (358258)	Bortezomib (L01XG01)
Bosutinib	Bosulif	General	Bosutinib (1307619)	Bosutinib (L01EA04)
Capecitabine	Xeloda, Xitabin, Kapetral	Anti-metabolites	Capecitabine (194000)	Capecitabine (L01BC06)
Carmustine	BiCNU, Gliadel	General	Carmustine (2105)	Carmustine (L01AD01)
Cladribine	Leustatin, Mavenclad	General	Cladribine (44157)	Cladribine (L01BB04)
Clofarabine	Clolar, Evoltra	Anti-metabolites	Clofarabine (44151)	Clofarabine (L01BB06)
Alkylating agents				
Bendamustine	Belrapzo, Bendeka, Treanda, Treakisym	–	Bendamustine (134547)	Bendamustine (L01AA09)
Busulfan	Busulfex, Myleran, Busilvex	–	Busulfan (1828)	Busulfan (L01AB01)
Carboplatin	Paraplatin	–	Carboplatin (40048)	Carboplatin (L01XA02)
Chlorambucil	Leukeran	–	Chlorambucil (2346)	Chlorambucil (L01AA02)
Cisplatin	Platinol	–	Cisplatin (2555)	Cisplatin (L01XA01)

ATC, Anatomical Therapeutic Chemical.

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