

Can mAb dose selection in IBD be supported by public domain data from other immune-mediated inflammatory diseases?



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Background

Biologics and small-molecule drugs have proven efficacy across many disease states and have revolutionized the treatment of immune-mediated inflammatory diseases (IMIDs) with ostensibly unrelated conditions but sharing multiple common inflammatory pathways, including inflammatory bowel disease (IBD), and other IMIDs [1,2]. Multiple therapies and biosimilars have been approved across IMID indications by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) [3]. A framework was developed to compare dose regimens studied for the treatment of IBD compared to other IMID indications based on public domain data. The objective was to explore clinically studied and regulatory approved treatment regimens across various drugs and drug classes in IBD vs non-IBD IMID indications, with the aim to support and guide drug development.

Methods

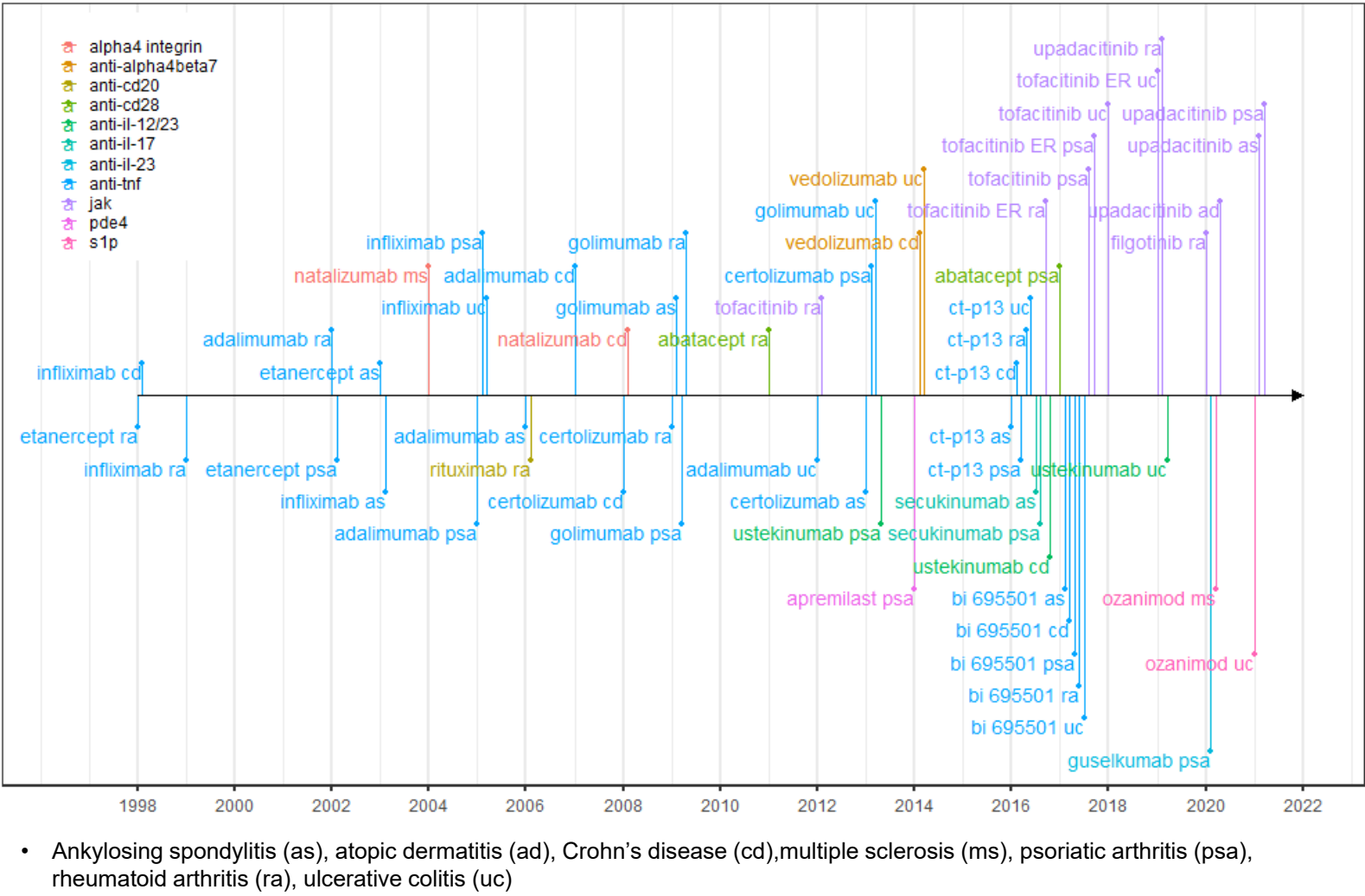
Certara’s clinical trial outcome databases were used as data sources in the analysis (supported by GlaxoSmithKline) [4]. The databases included summary level clinical data across 7 IMIDs: Crohn’s disease (CD), ulcerative colitis (UC), atopic dermatitis (AD), ankylosing spondylitis (AS), multiple sclerosis (MS), psoriatic arthritis (PsA), and rheumatoid arthritis (RA) [4]. Among 61 drugs studied in IBD (either CD or UC or both), 30 drugs of those that were studied in at least 2 IMID indications were selected for inclusion in the analysis (Table 1). Reported dose levels and dosing frequencies were normalized to standardized dosing regimens for each drug and data was further differentiated by treatment phase (e.g. induction vs maintenance phase in IBD), in order to best compare dose regimens across IMIDs. The relative dose studied in IBD vs non-IBD indications was estimated based on all pairwise comparisons across IBD and non-IBD studies. The development trajectory, as well as normalized absolute dose and dose ratio of these 30 drugs were explored and compared between immunology indications (AD, AS, MS, PsA and RA).

Table 1. Summary of 30 drugs studied in IBD

class	drug	indication	study	approved indication*	approved year
alpha4 integrin inhibitor	natalizumab	cd, ms	29	cd, ms	2004 to 2008
anti-alpha4beta7 integrin	abrilumab	cd, uc	15	/	/
	vedolizumab	cd, uc	27	cd, uc	2014 to 2014
anti-cd20	rituximab	ms, ra, uc	49	ra	2006 to 2006
anti-cd28	abatacept	cd, psa, ra, uc	70	psa, ra	2005 to 2017
anti-il-12/23	ustekinumab	ad, as, cd, ms, psa, ra, uc	59	cd, psa, uc	2013 to 2019
anti-il-17	brodalumab	as, cd, psa, ra	14	/	/
	secukinumab	ad, as, cd, ms, psa, ra	82	as, psa	2016 to 2016
	brazikumab**	cd	9	/	/
anti-il-23	guselkumab	cd, psa, ra	14	psa	2020 to 2020
	risankizumab	cd, psa	6	/	/
anti-il-6	pf-04236921	cd, ra	8	/	/
anti-ip-10	eldelumab	cd, uc	5	/	/
	adalimumab	as, cd, psa, ra, uc	149	as, cd, psa, ra, uc	2002 to 2012
	bi 695501	as, cd, psa, ra, uc	11	as, cd, psa, ra, uc	2017 to 2017
	certolizumab	as, cd, psa, ra	64	as, cd, psa, ra	2008 to 2013
	etanercept	as, cd, psa, ra	103	as, psa, ra	1998 to 2003
	golimumab	as, psa, ra, uc	60	as, psa, ra, uc	2009 to 2013
	infliximab	as, cd, psa, ra, uc	110	as, cd, psa, ra, uc	1998 to 2005
	ct-p13***	as, cd, psa, ra, uc	13	as, cd, psa, ra, uc	2016 to 2016
icam-1 inhibitor	alicaforfen	cd, uc	21	/	/
il-23p19	mirikizumab	cd, uc	9	/	/
	filgotinib	as, cd, psa, ra, uc	32	ra	2020 to 2020
	peficitinib	ra, uc	28	/	/
jak inhibitor	tofacitinib	ad, as, cd, psa, ra, uc	113	psa, ra, uc	2012 to 2018
	tofacitinib ER	psa, ra, uc	4	psa, ra, uc	2016 to 2019
	upadacitinib	ad, as, cd, psa, ra, uc	56	ad, as, psa, ra	2019 to 2021
pde4 inhibitor	apremilast	ad, as, psa, ra, uc	33	psa	2014 to 2014
s1p receptor modulator	amiselimod	cd, ms	11	/	/
	ozanimod	ms, uc	12	ms, uc	2020 to 2021

Ankylosing spondylitis (as), atopic dermatitis (ad), Crohn’s disease (cd),multiple sclerosis (ms), psoriatic arthritis (psa), rheumatoid arthritis (ra), ulcerative colitis (uc)
*FDA and/or EMA approval; **Brazikumab is included as additional drug of interests; ***Biosimilar of infliximab

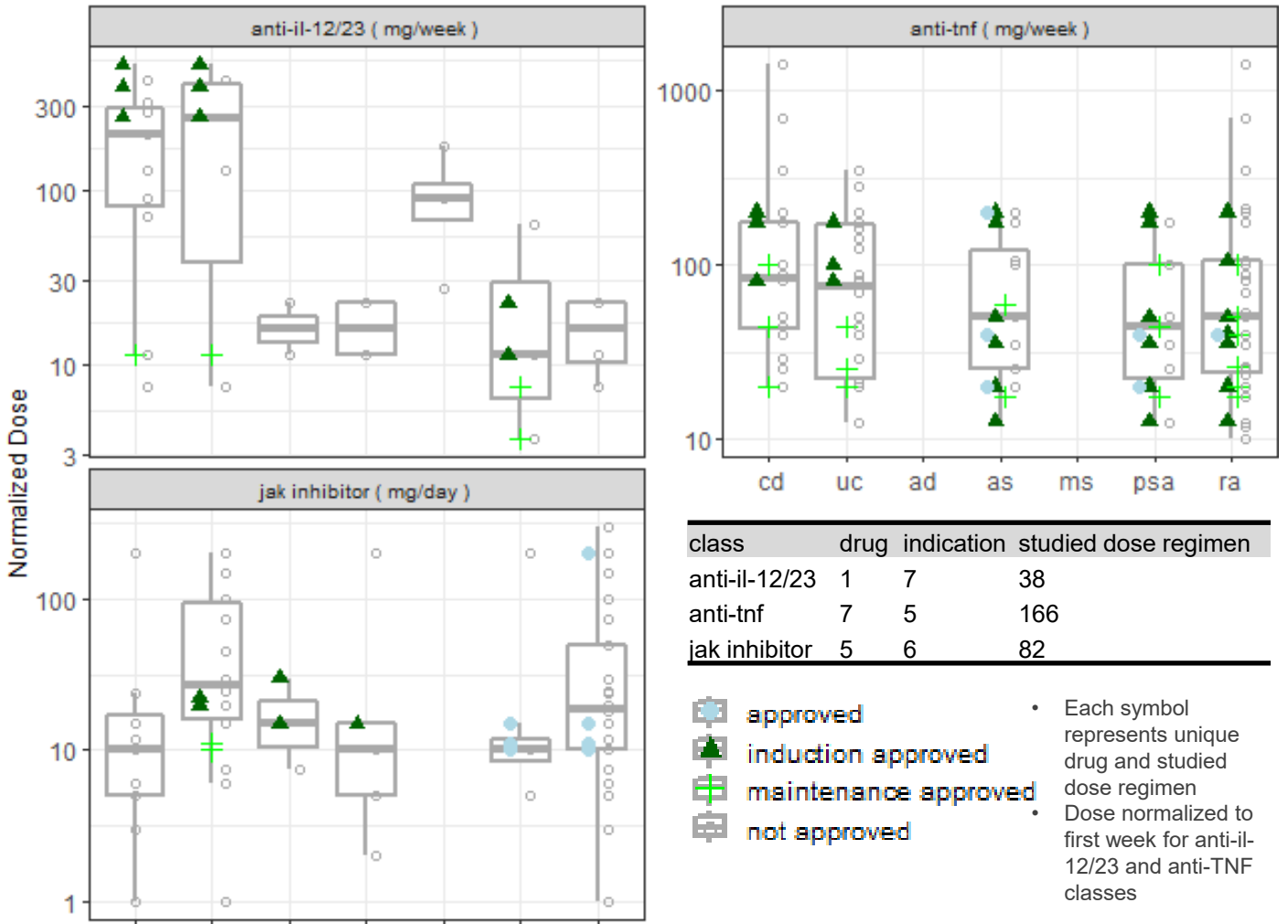
Figure 1. Approval timeline of 20 drugs across 7 IMIDs



Results

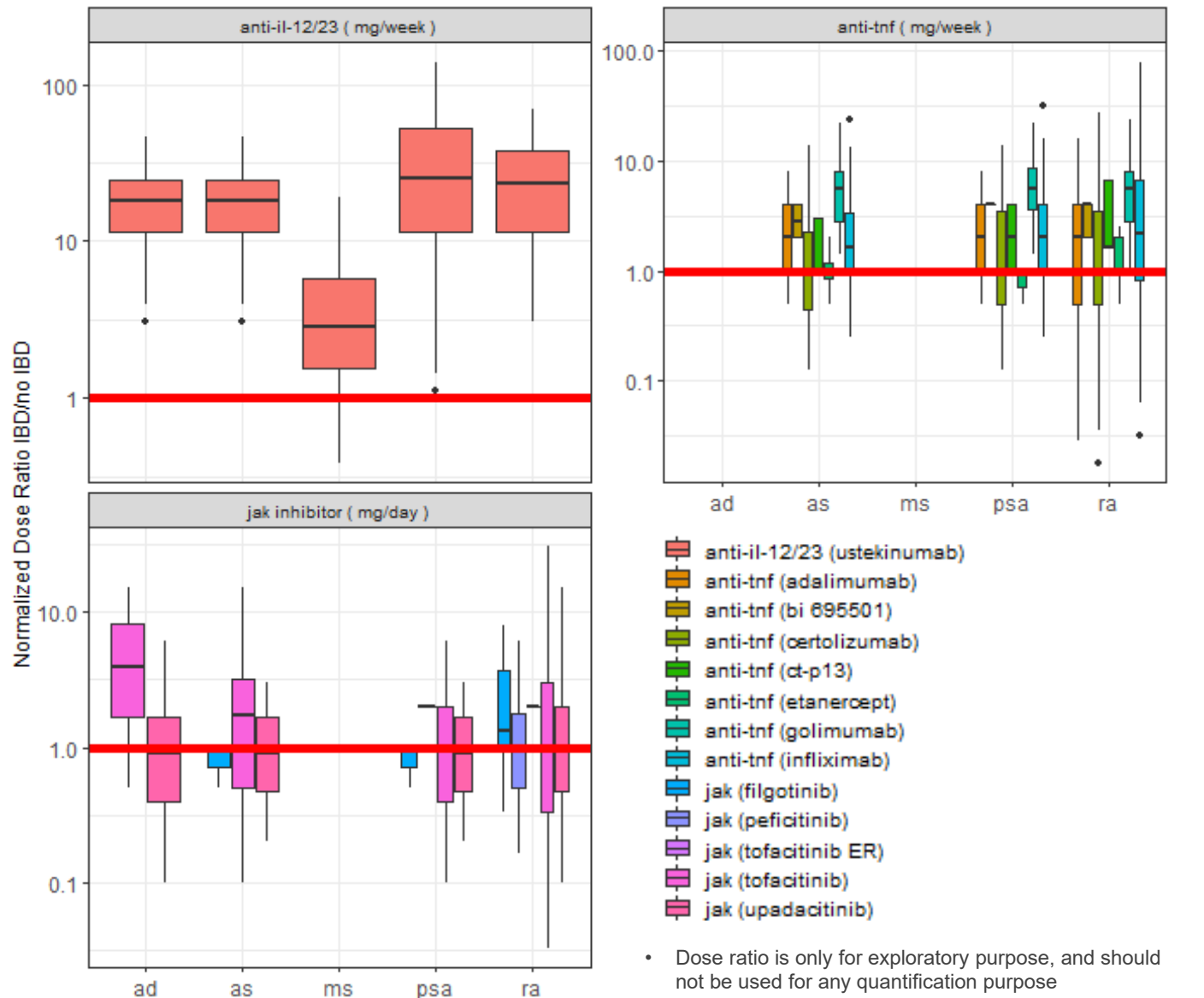
Twenty drugs out of selected 30 drugs were approved in at least one IMID, and 17 drugs were approved in at least 2 IMIDs (Table 1). Most anti-TNF drugs were approved in more than 4 IMIDs. Regulatory approval in several IMIDs was quite common and occurred more frequently in the past 10 years (Figure 1). Generally, slightly higher doses were studied and approved in IBD compared to non-IBD indications, especially for biological agents. Figure 2 illustrates normalized absolute dose across three selected classes: anti-il 12/23 inhibitor, anti-TNF and JAK inhibitor, respectively.

Figure 2 Normalized absolute dose across three drug classes: anti-il 12/23 inhibitor, anti-TNF and JAK inhibitor



In order to better compare the administrated induction dose across drugs and indications, ratios between normalized dose in IBD to non-IBD indications were further explored. A ratio above 1 indicated a higher dose in IBD compared to non-IBD indications (Figure 3).

Figure 3. Normalized induction dose ratio of anti-il 12/23, anti-TNF, and JAK inhibitor drugs in IBD vs non-IBD indications



Conclusions

In general, relatively wider dose ranges and higher doses are studied in IBD compared to other IMID indications, particularly for biological agents. Exploration of public domain and summary level data can provide an initial understanding of dosing regimens in clinical studies across multiple therapeutic indications which share similar disease pathogenesis. This analysis can be generalized as an empirical framework to support dose bridging across indications.

References

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