Title

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Journal

Clinical Gastroenterology and Hepatology, 20(2)

ISSN

1542-3565

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Publication Date

2022-02-01

DOI

10.1016/j.cgh.2021.01.006

Peer reviewed

HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2023 February 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2022 February ; 20(2): 465–467.e2. doi:10.1016/j.cgh.2021.01.006.

Patients with Low Drug Levels or Antibodies to a Prior Anti-TNF Are More Likely to Develop Antibodies to a Subsequent Anti-TNF

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Keywords

Crohn’s disease; IBD; pharmacokinetics; therapeutic drug monitoring; ulcerative colitis

INTRODUCTION

Therapeutic drug monitoring (TDM) with measurement of serum drug and anti-drug antibodies (ADAb) is used widely to confirm therapeutic exposure, rule out immunogenicity and optimize treatment of biologics in patients with inflammatory bowel diseases (IBD).[1] A recent genome-wide association study found the variant HLA-DQA1*05 to increase the risk of development of antibodies against infliximab (IFX) and adalimumab (ADM) twofold, regardless of concomitant immunomodulator use.[2, 3] However, there is currently limited evidence showing whether patients who develop antibodies to one anti-TNF are prone to develop antibodies to the subsequent anti-TNF. Our aim was to investigate the risk of subsequent antibody development in cases (with ADAb to prior anti-TNF) vs. controls

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AUTHOR CONTRIBUTIONS: All authors have approved the final draft submitted. Study concept, design, and supervision: NVC, AJ, ASC; data acquisition: LO, LY, AJ; statistical analysis: NVC, LO, LY, AJ; drafting of manuscript: NVC, FR; interpretation, critical revisions, and final approval: all authors

(without ADAb to prior anti-TNF) using a large cohort of patients with IBD who underwent TDM with a drug tolerant assay. Methods are described in the Supplements.

RESULTS

Our study included 5,828 subjects of whom 3,616/5,828 (62.0%) were first treated with IFX and then ADM and 2,212/5,828 (38.0%) were first treated with ADM and then IFX (Supplementary Table 1).

Survival analysis showed that in patients who switched from IFX to ADM, ADAb to IFX was significantly associated with subsequent ADAb formation to ADM ($p<0.0001$) (Figure 1A), with 28.5% of cases who developed ADAb to ADM vs. 12.4% of controls (hazards ratio [HR], 2.82; 95% confidence interval [CI], 2.35-3.38; $p<0.0001$) (Figure 1B). Increasing concentrations of ADAb to IFX were associated with higher proportions of patients developing ADAb to ADM ($p<0.0001$). ADAb concentrations ≥10 U/mL were associated with a higher proportion of patients developing ADAb to ADM after switch vs. those who had ADAb to IFX concentrations <10 U/mL (31.2% vs 21.5% respectively, $p<0.0001$). In patients who switched from ADM to IFX, survival analysis showed that ADAb to ADM was significantly associated with subsequent ADAb formation to IFX ($P<0.0001$) (Figure 1C), with 39.1% of cases who developed ADAb to IFX vs. 15.8% of controls (HR, 3.43; 95% CI, 2.81-4.20; $p<0.0001$) (Figure 1D). In contrast to patients switching from IFX to ADM, increasing concentrations of ADAb to ADM did not result in a significantly higher proportion of patients developing ADAb to IFX.

Prior to switch from IFX to ADM, median (IQR) IFX serum concentrations were lower in cases vs. controls [1.0 μg/mL (1.0-1.0) vs 11.7 μg/mL (4.2-27.1); $p <0.0001$]. Interestingly, even within the control group, lower IFX concentrations were associated with subsequent ADAb formation to ADM ($p <0.01$). Prior to switch from ADM to IFX, median (IQR) ADM serum concentrations were lower in cases vs. controls [1.6 μg/mL (1.6-3.0) vs 9.2 μg/mL (5.7-13.9); $p <0.0001$]. Similarly, even within the control group, lower ADM concentrations were associated with subsequent ADAb formation to IFX ($p <0.01$). Survival analysis showed that an IFX concentration ≤5 μg/mL was significantly associated with subsequent ADAb formation to ADM ($P<0.0001$) whereas an ADM concentration ≤7.5 μg/mL was significantly associated with subsequent ADAb formation to IFX ($P<0.0001$).

DISCUSSION

In this large retrospective case-control study including several thousand patients with IBD treated with anti-TNF, the risk for ADAb to ADM was 2-fold higher when patients had prior antibodies to IFX and the risk for ADAb to IFX was 3-fold higher when patients had prior antibodies to ADM. One hypothesis is that subjects who developed antibodies to the prior and subsequent anti-TNF have a genetic predisposition for developing ADAb.[2] Alternatively, since we found that subtherapeutic drug concentrations to the prior anti-TNF are associated with antibody formation to the subsequent anti-TNF, even in controls, one cannot rule out that these subjects suffer from accelerated drug clearance because of common mechanisms that influence anti-TNF pharmacokinetics, which may lead to low

drug concentrations and subsequent immunogenicity.[4, 5] A RCT in patients switching anti-TNFs because of antibodies demonstrated that start of the second anti-TNF in combination with an immunomodulator leads to lower rates of clinical failure and more favorable pharmacokinetics, compared to monotherapy.[6] Alternatively, a strategy with optimized monotherapy using proactive TDM may be effective as well, but remains to be assessed in a prospective manner.[7, 8] Our retrospective study has limitations as the lack of clinical data did not allow us to study confounding factors that may affect the factors influencing antibody formation and the lack of patient-relevant clinical outcomes limits its generalizability.

In conclusion, we observed a higher likelihood of developing antibodies to a subsequent anti-TNF in patients who developed antibodies to, or had subtherapeutic drug concentrations of the prior anti-TNF. Starting combination therapy and/or conducting proactive TDM should be considered in patients positive for antibodies when switching to another anti-TNF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FUNDING SUPPORT: TDM testing was performed by Prometheus Biosciences. KP was funded by the Ruth L. Kirschstein NRSA Institutional Research Training Grant (5T32DK007760-18). NVC holds a Research Scholar Award from the American Gastroenterological Association. The study was supported in part by the Digestive Diseases Research Center grant NIH DK120515.

CONCLICT OF INTEREST AND DISCLOSURES:

NVC: research grants from R-Biopharm, grants and personal fees from Takeda and UCB, personal fees from Celltrion and Prometheus. **MTA**: Consulting/Advisory Board of Boehringer Ingelheim, Gilead, Landos Biopharma, Teaching/Lecturing for Cornerstones Health, Inc., Focus Medical Communications, Imedex, Janssen Pharmaceuticals, Grants from Pfizer, Prometheus Laboratories Inc., Takeda Pharmaceuticals, **SF**: no disclosures, **KP**: no disclosures, **FR**: Consulting or AdBoard for Agomab, Allergan, AbbVie, Boehringer-Ingelheim, Celgene, Cowen, Genentech, Gilead, Gossamer, Guidepoint, Helmsley, Index Pharma, Jannsen, Koutif, Metacrine, Morphic, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Takeda, Techlab, Thetis, UCB, Grants from NIH, Helmsley Charitable Trust, Crohn's and Colitis Foundation, Department of Defense, UCB, Pliant, BMS, Pfizer, Boehringer Ingelheim, Morphic, Kenneth Rainin Foundation, **MSS**: Speaker, advisory board member, research and/or consultant for AbbVie, Janssen, Prometheus, Takeda, Pfizer, Ferring, Gilead, Amgen, Novartis, Lilly: **RK**: Speaker, advisory board member, and or clinical investigator for AbbVie, Encycle, Gilead, Innomar, Janssen, Lilly, Merck, Pfizer, Pendopharm, Robarts Clinical Trials, Roche/Genetec, Shire, Takeda., **LO**, **LY**, and **AJ** are employees of and own stock options for Prometheus Biosciences, **ASC**: Consulting Abbvie, Janssen, Takeda, Pfizer, Samsung, Arena, Prometheus, Bacainn; Research support Inform Diagnostics

REFERENCES

1. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S, American Gastroenterological Association Institute Clinical Guidelines C. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. Sep 2017;153(3):827–834. doi:10.1053/j.gastro.2017.07.032 [PubMed: 28780013]
2. Sazonovs A, Kennedy NA, Moutsianas L, et al. HLA-DQA1*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease. Gastroenterology. Jan 2020;158(1):189–199. doi:10.1053/j.gastro.2019.09.041 [PubMed: 31600487]
3. Wilson A, Peel C, Wang Q, Pananos AD, Kim RB. HLADQA1*05 genotype predicts anti-drug antibody formation and loss of response during infliximab therapy for inflammatory bowel disease. Aliment Pharmacol Ther. Feb 2020;51(3):356–363. doi:10.1111/apt.15563 [PubMed: 31650614]

4. Vande Casteele N, Gils A, Singh S, et al. Antibody Response to Infliximab and its Impact on Pharmacokinetics can be Transient. Am J Gastroenterol. Jun 2013;108(6):962–71. doi:10.1038/ajg.2013.12 [PubMed: 23419382]
5. Lefevre PLC, Shackelton LM, Vande Casteele N. Factors Influencing Drug Disposition of Monoclonal Antibodies in Inflammatory Bowel Disease: Implications for Personalized Medicine. BioDrugs. Oct 2019;33(5):453–468. doi:10.1007/s40259-019-00366-1 [PubMed: 31301024]
6. Roblin X, Williet N, Boschetti G, et al. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial. Gut. Jul 2020;69(7):1206–1212. doi:10.1136/gutjnl-2019-319758 [PubMed: 31980448]
7. Lega S, Phan BL, Rosenthal CJ, et al. Proactively Optimized Infliximab Monotherapy Is as Effective as Combination Therapy in IBD. Inflamm Bowel Dis. Jan 1 2019;25(1):134–141. doi:10.1093/ibd/izy203 [PubMed: 29868777]
8. Drobne D, Kurent T, Golob S, et al. Optimised infliximab monotherapy is as effective as optimised combination therapy, but is associated with higher drug consumption in inflammatory bowel disease. Aliment Pharmacol Ther. Apr 2019;49(7):880–889. doi:10.1111/apt.15179 [PubMed: 30784100]

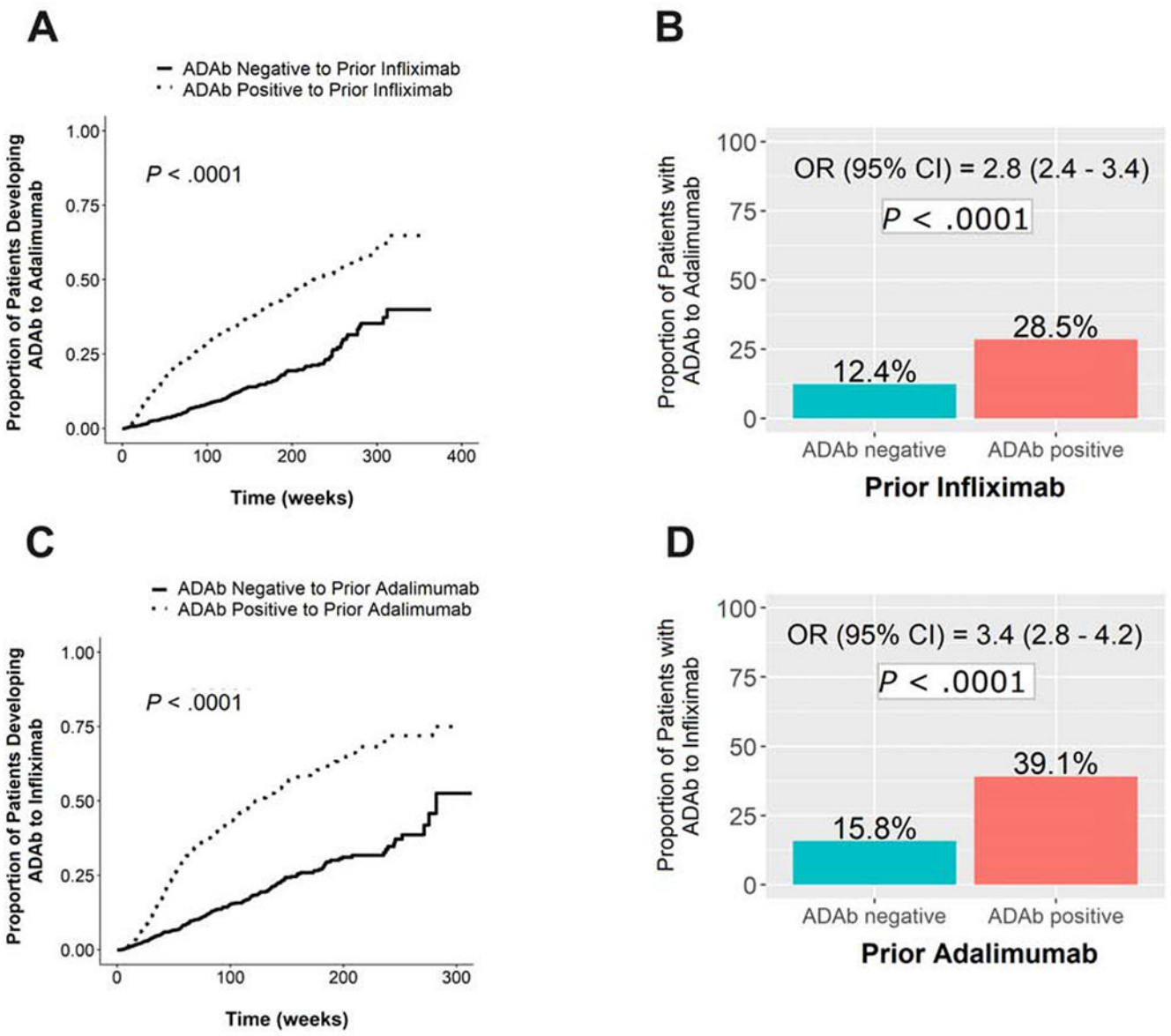

Figure 1.

Kaplan-Meier curves representing proportion of patients who developed anti-drug antibodies (ADAb) when (A) switched from infliximab to adalimumab and (C) switched from adalimumab to infliximab. Difference in rate of ADAb formation between cases and controls for those patients who (B) switched from infliximab to adalimumab and (D) switched from adalimumab to infliximab. Cases = dotted line; controls = bold line.