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IL-28B polymorphisms and the response to antiviral therapy in HCV genotype 2 and 3 varies by ethnicity: a meta-analysis

A. S. Rangnekar and R. J. Fontana *Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA*

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SUMMARY. Studies of IL-28B genotype in patients with hepatitis C virus (HCV) genotype 2/3 infection have yielded conflicting results. The aim of this meta-analysis was to obtain a pooled odds ratio (OR) of the impact of IL-28B genotype on achieving sustained virologic response (SVR) in patients with HCV genotype 2/3 infection treated with pegIFN and ribavirin. A meta-analysis with a random effects model was performed, and study heterogeneity and publication bias were assessed. Forty-three percent of the Caucasians (11 studies) and 86% of Asians (five studies) had the favourable IL-28B genotype. In Caucasians, the pooled OR of SVR with the favourable IL-28B genotype was 1.36 (95%CI: 0.98–1.88, $P = 0.07$) in all patients and 1.55 (95%CI: 1.10–2.18, $P = 0.01$) in patients treated with pegIFN and ribavirin for ≥ 24 weeks. In Asians, the pooled OR of SVR in patients with the favourable IL-28B genotype was 1.99 (95%CI: 0.94–4.25, $P = 0.07$). The favourable IL-28B genotype was also significantly associated with rapid virologic response (RVR) in both groups (Caucasians: OR: 1.82, 95%CI: 1.12–2.96, $P = 0.02$; Asians: 2.39, 95%CI: 1.39–4.11, $P = 0.002$), as well as the likelihood of an SVR in a subgroup of 350 Caucasian patients without an RVR (OR: 3.29, 95%CI: 1.67–6.51, $P = 0.001$). The favourable IL-28B genotype is a statistically significant predictor of SVR and RVR in Caucasian patients treated with pegIFN and ribavirin for 24 weeks. In contrast, the favourable IL-28B genotype is associated with RVR, but not SVR in Asian HCV genotype 2 patients.

Keywords: genetic polymorphisms, hepatitis C, peginterferon, ribavirin, sustained virologic response.

INTRODUCTION

A single nucleotide polymorphism (SNP) upstream of the interleukin 28B (*IL-28B*) gene is associated with hepatic responsiveness to interferon therapy in hepatitis C virus (HCV) genotype 1 patients [1]. The highly variable prevalence of the favourable IL-28B genotype in patients of varying ethnicity, in part, explains differences in the observed sustained virologic response (SVR) rates. Although other host, viral and treatment factors may influence a patient's chance of SVR, the favourable IL-28B genotype is the single most important pretreatment predictor of achieving SVR with peginterferon (pegIFN) and ribavirin therapy in genotype 1 patients [2]. In contrast, the association of IL-28B and SVR in patients with HCV genotype 2/3 infection remains unclear [3–5].

Although patients with HCV genotype 2/3 are more responsive to pegIFN and ribavirin, up to 30% of treated patients will not achieve SVR [6]. Furthermore, the new direct acting antiviral agents (DAAs), boceprevir and telaprevir, are not approved for the use in patients with HCV genotype 2/3 infection [7]. As such, pegIFN and ribavirin remain the only currently approved treatment for these patients. This meta-analysis was undertaken to better quantify the effect of the favourable IL-28B genotype on achieving SVR after treatment with pegIFN and ribavirin in patients with chronic HCV genotype 2/3 infection. In addition, the effect of IL-28B on achieving a week 4 rapid virologic response (RVR) as well as the impact of patient ethnicity on SVR was evaluated.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; CI, Confidence interval; DAA, Direct acting antiviral agent; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; IL-28B, Interleukin 28B; OR, Odds ratio; PCR, Polymerase chain reaction; pegIFN, Peginterferon; RVR, Rapid virologic response; SNP, Single nucleotide polymorphism; SVR, Sustained virologic response.

Correspondence: Robert J. Fontana, MD, 3912 Taubman Center, Ann Arbor, MI 48109-0362, USA.
E-mail: rfontana@med.umich.edu

MATERIALS AND METHODS

Literature search

A search of the MEDLINE, PUBMED and EMBASE computer databases was performed of manuscripts published between

January 2000 and January 2012, using the text words IL-28B, IL28B, IL28 and interleukin 28. Additional electronic and manual searches of abstracts presented at the American Association for the Study of Liver Diseases and American Gastroenterological Association meetings were undertaken from 2007 to 2012. Finally, consultation with expert hepatologists and recursive manual searches of references from published studies were performed.

Study selection criteria

Criteria for study inclusion were as follows: (i) published studies of IL-28B genotyping in adults with HCV genotype 2 or 3 infection; (ii) treatment with pegIFN and ribavirin and (iii) a reported outcome of SVR. All published studies were included regardless of sample size, but studies published solely as abstracts were excluded due to a lack of extractable data for SVR stratified by IL-28B genotype. The following exclusion criteria were applied: (i) human immunodeficiency virus (HIV) co-infection, (ii) prior liver transplantation, (iii) use of DAAs and (iv) use of IL-28B SNPs other than rs12979860 or rs8099917. After reviewing all citations identified in the literature search, two investigators (AS, RF) independently applied these selection criteria and extracted data. Any disagreements were resolved by consensus.

Data extraction

All eligible studies were reviewed in an independent and duplicate manner by both investigators (AS, RF). For each study, the following data were collected: (i) Study: year, location, design, publication status; (ii) Patient factors: number, mean age, baseline serum aspartate aminotransferase (AST), baseline alanine aminotransferase (ALT), body mass index (BMI) and percentage with diabetes mellitus, male gender, treatment naïve and HIV co-infection; (iii) HCV factors: HCV genotype, baseline HCV RNA level, number of patients achieving RVR and SVR; (iv) Treatment factors: duration of pegIFN and ribavirin, type of pegIFN, dose reduction of antiviral medications, use of growth factors; and (v) IL-28B: IL-28B SNP tested and number with each IL-28B genotype who achieved RVR and SVR. Discrepancies in data extraction were resolved by discussion between the investigators.

IL-28B testing

The two IL-28B SNPs reported in the individual studies were rs12979860 and rs8099917. The favourable genotype for rs12979860 is CC, while the unfavourable genotypes are CT and TT. The favourable genotype for rs8099917 is TT, while the unfavourable genotypes are TG and GG.

Primary outcome

The primary outcome measure was achievement of SVR after pegIFN and ribavirin treatment, defined as undetectable serum HCV RNA by polymerase chain reaction (PCR) testing 24 weeks after treatment.

Secondary outcome

A secondary outcome measure was achievement of RVR with pegIFN and ribavirin treatment, defined as an undetectable serum HCV RNA at week 4.

Quality assessment

Study quality was assessed using an 8-item scoring system based on previously validated tools that focused on study

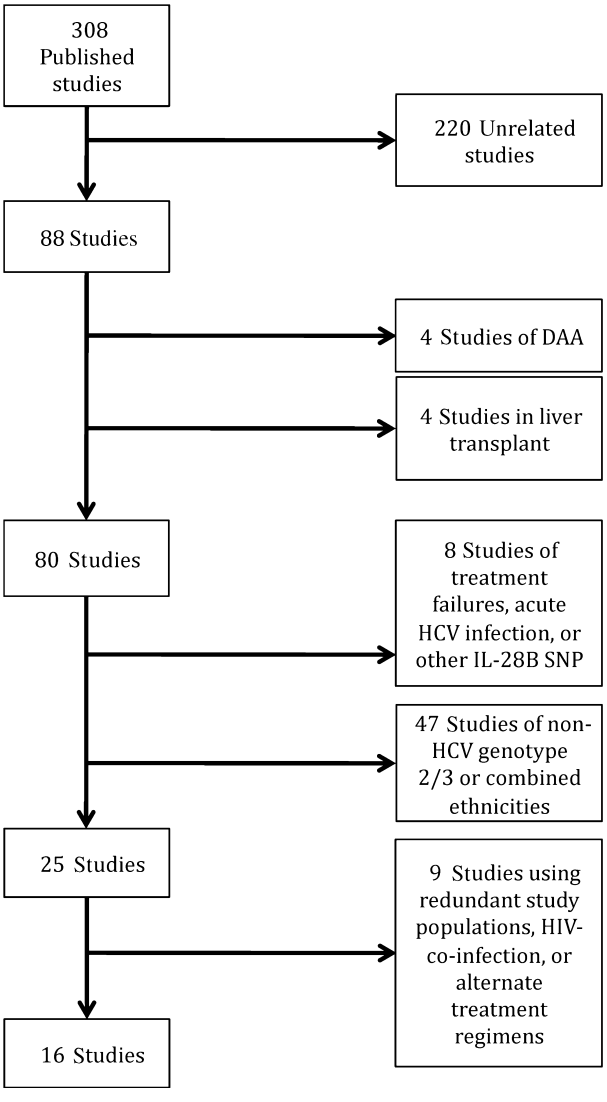

Fig. 1 Study selection overview. From a total of 308 studies, 16 studies met the inclusion criteria.

Table 1 Summary of individual studies of IL-28B genotype included in the meta-analysis

Study	*N*	Age (mean)	Male (%)	BMI (kg/m^2)	Advanced fibrosis (%)*	Treatment duration (weeks)	Prevalence of favorable IL-28B genotype (%)	SVR in favorable IL-28B genotype (%)	SVR in unfavorable IL-28B genotype (%)
Caucasian									
Stattermayer (Austria)	208	39	60	n/a	89	24	42	81	74
Mangia (Italy)	268	n/a†	58	n/a‡	19	12–24	37	82	71
Sarrazin (Germany)	205	46	54	n/a	30	24–48	42	87	71
Bochud (Europe/Israel)	71	43	61	25	41	24–72	64	89	85
Moghaddam (Europe)	281	38	59	n/a	n/a	14–24	46	77	84
Fattovich (Italy)	159	46	55	25	24	24	39	92	90
Bitetto (Italy)	101	47	52	24	n/a	24	44	82	89
de Rueda (Spain)	50	n/a§	58	n/a	23	48	50	84	80
Amanzada (Germany)	47	49	77	n/a	n/a	24–48	51	83	83
Halfon (France)	42	47	71	n/a	38	24	36	80	70
Lindh (Europe)	166	42	60	26	13	12–24	40	85	75
Total	1599	43	55%		24%		43%	83%	78%
Asian									
Kawaoka (Japan)	130	57	56	23	17	24	82	78	67
Yu (Taiwan)	482	53	55	n/a	28	24	90	89	86
Sakamoto (Japan)	129	64	50	24	11	24	78	81	59
Sinn (Korea)	63	57	53	n/a	61	24	86	80	100
Ochi (Taiwan)	29	49	62	n/a	n/a	24–48	90	92	33
Total	833	55	55%		22%		86%	86%	75%

SVR, sustained virologic response.
*Not all patients in each study underwent liver biopsy. In most studies, advanced fibrosis defined as Ishak score >4, METAVIR score >3, or Scheur >F3. †78% of patients with age > 40 years. ‡42% of patients with BMI > 27 kg/m2. §62% of patients with age > 40 years.

design, population homogeneity and potential study biases [8,9]. High quality was defined by a score of ≥ 6 (Table 2).

Statistical analysis

The estimate of effect was a pooled odds ratio (OR) determined using the DerSimonian and Laird method for a random effects model. Study heterogeneity was assessed by the I^2 test, with $I^2 > 50\%$ suggesting substantial heterogeneity. Publication bias was assessed through the Harbord and Peters tests. Influence analysis was performed to determine whether a single study exerted undue influence. Data from the included studies were analysed separately by patient race. Sensitivity and subgroup analyses were performed based on treatment algorithm, prior treatment and study quality score. All statistics were computed using STATA 11.0 (StataCorp LP, College Station, TX, USA).

RESULTS

An initial search revealed 308 studies of IL-28B among which 88 specifically evaluated virologic outcomes in treated patients An additional 63 studies were excluded due to the inclusion of previously treated patients, acute HCV infection, use of alternative IL-28B SNPs, use of DAAs, inclusion of liver transplant recipients, combined ethnicities or nongenotype 2/3 patients. Of the remaining 25 studies, nine were excluded due to redundant study populations, HIV co-infection or use of alternative treatment regimens, leaving 16 studies in the current analysis (Fig. 1).

Caucasians with HCV genotype 2/3

SVR outcome

There were 11 studies of Caucasians with HCV genotype 2/3 [3,10–19]. Among 1599 patients, 43% had the favourable

Table 2 Individual Study quality score checklist

Study	All pts from prospective study*	Treatment ≥ 24 weeks	Ribavirin dose >800 mg/day*	All pts receive same pegIFN*	100% pts treatment naive*	All pts from original study genotyped for IL-28B*	Reporting of ≥ 4 pre-treatment predictors of SVR†	Most robust IL-28B SNP for race used‡	Total score	Quality§
Caucasian										
Stattermayer	N	Y	N	Y	Y	N	Y	Y	5	Low
Mangia	Y	N	Y	Y	Y	N	Y	Y	6	High
Sarrazin	N	Y	N	N	N	Y	Y	Y	4	Low
Bochud	Y	Y	Y	Y	Y	N	Y	Y	7	High
Moghaddam	Y	N	Y	Y	Y	N	N	Y	5	Low
Fattovich	Y	Y	Y	N	Y	Y	Y	Y	7	High
Bitetto	N	Y	Y	N	Y	Y	Y	Y	6	High
de Rueda	N	Y	Y	Y	Y	Y	Y	Y	7	High
Amanzada	N	Y	N	N	N	Y	N	Y	3	Low
Halfon	N	Y	N	N	N	Y	Y	Y	4	Low
Lindh	Y	N	Y	Y	Y	N	Y	Y	6	High
Asian										
Kawaoka	N	Y	N	Y	Y	N	Y	Y	5	Low
Yu	N	Y	Y	N	Y	N	Y	Y	5	Low
Sakamoto	N	Y	Y	N	N	Y	Y	Y	5	Low
Sinn	Y	Y	Y	Y	N	Y	Y	Y	7	High
Ochi	N	Y	Y	Y	N	N	N	Y	4	Low

*Unknown = N.
†Age, gender, HCV RNA, BMI (or weight or presence of diabetes mellitus), liver fibrosis.
‡rs12979860 for Caucasians, rs8099917 for Asians.
§Score ≥ 6 denotes high quality.

IL-28B genotype CC at rs12979860 (Table 1). Overall, 83% of patients with the favourable IL-28B genotype achieved SVR as compared to 78% of patients with the unfavourable genotype, with a pooled OR of 1.36 (95%CI: 0.98–1.88, $P = 0.07$) with low heterogeneity between studies ($I^2 = 29\%$). In a subgroup analysis of eight studies that included only treatment naïve patients, the pooled OR of SVR was 1.21 (95%CI: 0.85–1.74, $P = 0.29$). Among the eight studies with pegIFN and ribavirin treatment for at least 24 weeks, the pooled OR of SVR was 1.55 (95%CI: 1.10–2.18, $P = 0.01$) as compared to 1.17 (95%CI: 0.53–2.58, $P = 0.70$) in the studies with variable duration treatment regimens. Among the four studies that used a ribavirin dose ≥ 800 mg/day for at least 24 weeks, the pooled OR of SVR was 1.02 (95%CI: 0.55–1.92, $P = 0.95$). The pooled OR was 1.49 (95%CI: 1.02–2.19, $P = 0.04$) in the six high-quality studies *vs* 1.33 (95%CI: 0.72–2.43, $P = 0.36$) in the five low-quality studies (Table 2).

RVR outcome

Six studies reported RVR data in 1265 Caucasian patients of which 42% had the favourable IL-28B genotype. Seventy-seven percent of patients with the favourable IL-28B achieved RVR as compared to 65% of patients with the unfavourable genotype, with a pooled OR of 1.82 (95%CI: 1.12–2.96, $P = 0.02$) and moderate heterogeneity between studies ($I^2 = 69\%$).

Among 350 patients who achieved RVR in three studies, 89% of 142 patients with the favourable IL-28B genotype and 85% of 208 patients with the unfavourable IL-28B genotype also achieved SVR (pooled OR: 1.37, 95%CI: 0.71–2.67, $P = 0.35$). In contrast, among 184 patients who did not achieve RVR, 78% of 68 patients with the favourable IL-28B and 50% of the 116 with the unfavourable IL-28B genotype achieved SVR (pooled OR: 3.29, 95% CI: 1.67–6.51, $P = 0.001$).

Asians with HCV genotype 2

SVR outcome

There were five studies [20–24] of 833 Asian patients with HCV genotype 2 infection, in which 86% had the favourable IL-28B genotype. Overall, 86% of patients with the favourable IL-28B genotype achieved SVR, while 75% of patients with the unfavourable IL-28B genotype achieved SVR with a pooled OR of 1.99 (95%CI: 0.94–4.25, $P = 0.07$). There was low to moderate heterogeneity between studies ($I^2 = 44\%$). In a subgroup analysis of the two studies that explicitly included only treatment naïve patients, the pooled OR of SVR was 1.54 (95%CI: 0.81–2.93, $P = 0.18$). Among the four low-quality studies, the pooled OR was 2.22 (95%CI: 01.14–4.35, $P = 0.02$).

RVR outcome

In the two studies reporting RVR data, 88% of the 594 patients had the favourable IL-28B genotype. Eighty-two percent of patients with the favourable IL-28B genotype and 62% of patients with the unfavourable genotype achieved RVR, with a pooled OR of RVR of 2.39 (95%CI: 1.39–4.11, $P = 0.002$).

Pooled analysis

After combining the 16 studies with 2432 patients, the pooled OR of SVR in patients with the favourable IL-28B genotype was 1.48 (95%CI: 1.09–2.02, $P = 0.01$). There

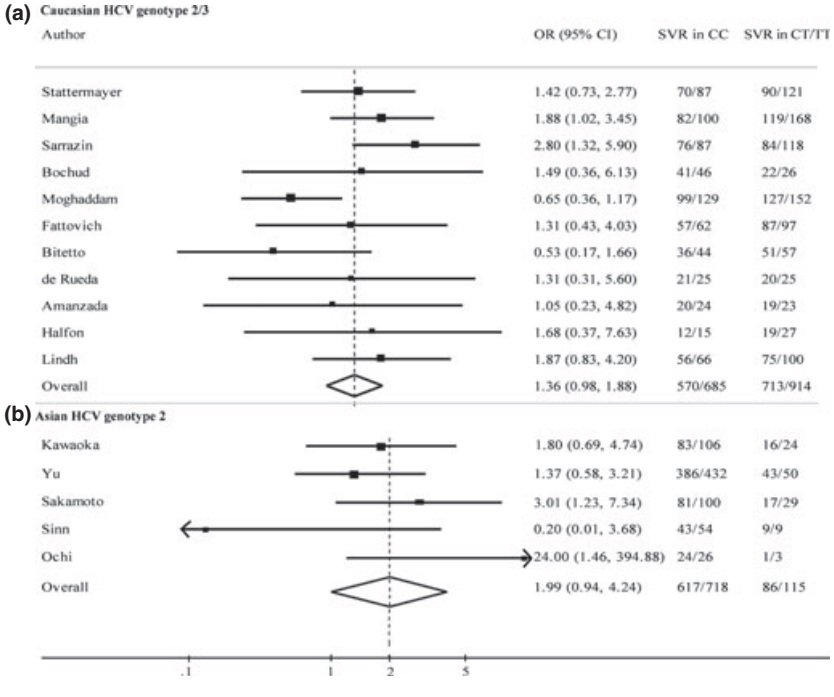

Fig. 2 Forest plots of IL-28B genotype and SVR in patients with hepatitis C virus (HCV) genotype 2/3 infection stratified by race. (A) There were 11 studies of 1599 Caucasian HCV genotype 2/3 patientsm and (B) there were five studies of 833 Asian HCV genotype 2 patients. SVR, sustained virologic response.

was low heterogeneity between studies (I^2 = 34%). The pooled OR was 1.27 (95%CI: 0.95–1.69, P = 0.11) in the 10 studies with only treatment naïve patients and 1.44 (95%CI: 0.98–2.11, P = 0.06) among the seven high-quality studies. There was no evidence of publication bias by the Harbord or Peters tests (P = 0.69 and P = 0.33, respectively).

DISCUSSION

While IL-28B genotyping has an important role in HCV genotype 1 patients treated with pegIFN and ribavirin, its value in HCV patients with genotype 2/3 remains less clear [2]. This meta-analysis demonstrates that the favourable IL-28B genotype is a significant predictor of SVR in Caucasian patients with HCV genotype 2/3 treated with pegIFN and ribavirin for 24 weeks. Additionally, IL-28B genotype may be predictive of SVR in Asian patients with HCV genotype 2, although the pooled OR of SVR did not reach statistical significance perhaps due to inadequate sample size (Fig. 2).

Our results also suggest that the favourable IL-28B genotype increases the odds of achieving RVR in Caucasian and Asian patients with HCV genotype 2/3 infection, a finding similar to that reported in HCV genotype 1 patients [2]. Furthermore, the results of this study demonstrate that IL-28B genotype may be helpful in stratifying the odds of SVR in patients with HCV genotype 2/3 who do not achieve RVR. Prior data suggest that HCV genotype 2/3 patients with low viral load who achieve RVR may be candidates for a shortened duration of therapy to 12–16 weeks [25,26]. However, it is unclear whether the favourable IL-28B genotype can be used to further identify patients from this group who are more likely to achieve SVR and/or are at lower risk of relapse. Individual studies have not found an association between IL-28B genotype and SVR rates in patients treated for <24 weeks after achieving RVR, but they may be underpowered [13,19]. Therefore, IL-28B testing may play an important role in counselling individual patients that are receiving antiviral therapy and particularly in those experiencing side effects who do not achieve RVR.

In the era of DAAs, IL-28B testing in HCV genotype 1 patients may be limited to specific populations in which DAAs are not yet approved, such as in those with HIV coinfection [2]. In contrast, pegIFN and ribavirin are the only currently approved agents for HCV genotype 2/3 infection. An improved ability to predict SVR may be particularly important for patients intolerant to this regimen, but the absolute difference in response rates in those with and without the favourable IL28-B genotype is small.

In contrast to our results, another recent meta-analysis of IL-28B testing and SVR in patients of combined HCV genotypes reports a statistically significant pooled OR of SVR in Asians with HCV genotype 2 infection [5], a finding likely due to the inclusion of only two Asian studies. Our own subgroup analysis of five Asian studies identified a strong trend which does not reach statistical significance. The meta-analysis by Chen *et al.* also demonstrates a lack of association between the favourable IL-28B genotype and SVR in Caucasian patients with HCV genotype 2/3, although only five studies were included. Assessing the role of IL-28B testing in nonCaucasian patients with HCV genotype 2/3 was limited in our study. Among the five pooled Asian studies, two explicitly included some treatment-experienced patients who may have reduced the impact of IL-28B genotyping in predicting SVR. In addition, there were no studies of HCV genotype 2/3 African American patients, a group with traditionally lower response to interferon. However, a substantially lower proportion of African Americans are infected with HCV genotype 2/3 in the general US population compared to Caucasians (i.e. 5% *vs* 20–30%) [27,28]. Because of the lack of stratification by HCV genotype in many studies, we were unable to determine whether IL-28B genotype has greater utility in patients with HCV genotype 2 *vs* 3. However, this issue is worthy of further study because HCV genotype 3 patients with a high baseline HCV RNA level are more prone to relapse after a 24-week course of treatment compared to those with HCV genotype 3 and low viral load or HCV genotype 2 infection [29]. Finally, how IL-28B testing fits in with other known pretreatment predictors of SVR remains unknown.

In conclusion, this meta-analysis demonstrates that the favourable IL-28B genotype is significantly associated with SVR in Caucasian patients with HCV genotype 2/3 infection treated with pegIFN and ribavirin for 24 weeks. However, the magnitude of the absolute difference in SVR rates (83% *vs* 78%) is small and may not influence the decision to initiate treatment. In addition, the favourable IL-28B genotype is associated with RVR as well as SVR in patients who do not achieve RVR, and this information may prove useful to clinicians when counselling individual patients during therapy.

AUTHOR CONTRIBUTIONS

Amol Rangnekar carried out study concept, design, data acquisition, analysis and interpretation, manuscript drafting and finalization, statistical analyses. Robert J. Fontana performed study concept, design, data acquisition, analysis and interpretation, manuscript drafting and finalization, overall supervision.

CONFLICT OF INTERESTS

Dr. Rangnekar has no financial conflicts of interest. Dr. Fontana has served as a consultant to Bristol-Meyers Squibb, Vertex Pharmaceuticals, Tibotec, Merck, GlaxoSmithkline and Medtronic in the past

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