A Narrative Review of Anti–SARS-CoV-2 Vaccines and Immune Thrombocytopenia: Be Aware, But Reassured

Marina Beltrami-Moreira, MD, PhD,[1] and James B. Bussel, MD[2]

[1]Division of Hematology/Oncology, NewYork-Presbyterian Hospital/Weill Cornell Medicine, New York, New York

[2]Division of Pediatric Hematology/Oncology, NewYork-Presbyterian Hospital/Weill Cornell Medicine, New York, New York

Corresponding author:
Marina Beltrami-Moreira, MD, PhD
NewYork-Presbyterian Hospital/
Weill Cornell Medicine
520 East 70th Street
Starr Pavilion, 3rd Floor
New York, NY 10065
Email: mab9624@nyp.org

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Abstract: ***Background:*** The COVID-19 pandemic gave rise to rapid development of anti–SARS-CoV-2 vaccines using established and new technologies. Immune thrombocytopenia (ITP) is a bleeding disorder that has been associated with COVID-19 vaccine products that are currently in use. We reviewed the available evidence regarding the most commonly used vaccines against SARS-CoV-2 in North America and Europe and their association with ITP. We found that population-based studies suggested a small increase in the incidence of ITP in persons receiving the ChAdOx1 nCoV-19 vaccine from Oxford-AstraZeneca, on the order of 6 cases per million doses administered. Severe bleeding was an even rarer event. Both messenger RNA–based and adenovirus-based vaccines have been associated with exacerbation of preexisting ITP in 6% to 20% of patients. ITP exacerbation is readily treatable with standard approaches when needed. Severe bleeding events are rare both in the general population and in persons with preexisting ITP, and overall, the benefits of vaccination outweigh the risks. Further identification of persons at the highest risk for complications (including those with ITP, vaccine-induced immune thrombotic thrombocytopenia, and myocarditis) and clear communication of both risks and benefits of immunization will continue to be paramount in the global campaign against COVID-19.

Introduction

According to the World Health Organization Coronavirus (COVID-19) Dashboard, more than 570 million confirmed cases of COVID-19 have occurred, including more than 6.4 million deaths as of August 4, 2022, and more than 12 billion vaccine doses have been given worldwide.[1] Anti-SARS-CoV-2 vaccines have decreased

Table 1. Characteristics of SARS-CoV-2 Vaccines Commonly Used in North America and Europe

Name	INN	Trade Name	Technology	Antigen	FDA Approval Status
Pfizer-BioNTech COVID-19 vaccine	Tozinameran	Comirnaty	Modified mRNA, lipid nanoparticle	Entire length of SARS-CoV-2 spike protein modified for improved expression and immunogenicity	Full approval
Moderna COVID-19 vaccine	Elasomeran	Spikevax	Modified mRNA, lipid nanoparticle	Optimized sequence encoding prefusion-stabilized SARS-CoV-2 spike protein	Full approval
Janssen COVID-19 vaccine	N/A	N/A	Replication-incompetent recombinant adenovirus type 26 vector	SARS-CoV-2 spike protein sequence	Use authorized[a]
Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine	N/A	Vaxzevria	Replication-deficient simian adenovirus vector	Full-length, codon-optimized spike protein of SARS-CoV-2 and a tissue plasminogen activator leader sequence	Not in use in the United States

[a]Use limited owing to association with vaccine-induced thrombotic thrombocytopenia.

FDA, US Food and Drug Administration; INN, international nonproprietary name; mRNA, messenger RNA; N/A, not applicable.

the number of severe COVID-19 cases and deaths; vaccination is the primary means by which the pandemic has been brought under the current level of control.[2-5] However, characteristics of certain vaccine formulations, and possibly of the SARS-CoV-2 spike antigen, have resulted in very rare but serious life-threatening adverse events, such as vaccine-induced immune thrombotic thrombocytopenia (VITT) and the usually less-severe immune thrombocytopenia (ITP).

One of the first fatalities temporally related to a SARS-CoV-2 vaccine was the case of a physician who died of an intracranial hemorrhage after developing severe ITP that was refractory to therapy.[6] This case and other reports led to scrutiny of incident ITP cases following SARS-CoV-2 vaccination and the effects of these immunizations on patients with preexisting ITP. Soon after, reports of VITT appeared from 3 countries in Europe.[7-9] Although these events are exceedingly rare, they are severe.

Vaccine safety data are of utmost relevance to addressing immunization hesitancy, which persists despite the dramatic consequences of a global pandemic. We offer an overview of the currently available evidence regarding incident ITP following administration of anti–SARS-CoV-2 vaccines, and outcomes of patients with preexisting ITP who receive immunization against COVID-19. This review does not encompass VITT, which has been extensively reviewed in the literature.

SARS-CoV-2 Vaccines in Current Use

The characteristics of the 4 most commonly used vaccines in North America and Europe are summarized in Table 1. On August 23, 2021, the US Food and Drug Administration (FDA) granted full approval to the first anti–COVID-19 vaccine, tozinameran (Comirnaty, Pfizer-BioNTech), which had previously received emergency use authorization.[10] The vaccine, which is generally known as the Pfizer vaccine, is based on messenger RNA (mRNA) containing 1-methyl-3'-pseudouridylyl instead of uridine bases. The mRNA encodes the entire length of the SARS-CoV-2 spike protein with modifications that improve protein expression and immunogenicity.[11] A lipid mix forms nanoparticles with the mRNA, allowing for its stabilization and delivery. In addition, the lipid mix acts as an adjuvant for the immune response. The mix contains a pegylated lipid (ALC-0159) and 3 other nonpegylated lipids (ALC-0315, distearoylphosphatidylcholine [DSPC], and cholesterol).[12]

Subsequently, on January 31, 2022, the FDA granted full approval to elasomeran (Spikevax, Moderna), which had previously received emergency use authorization. This nucleoside-modified mRNA vaccine, which is generally known as the Moderna vaccine, contains an optimized sequence encoding prefusion-stabilized SARS-CoV-2 spike protein.[13] The Moderna vaccine nanoparticles also contain cholesterol, a pegylated lipid, and 2 other lipids. Moderna's lipid mix also serves mRNA delivery and vaccine adjuvant purposes. Both the Pfizer and Moderna vaccines have received full FDA approval for the primary vaccination series and booster vaccination in adults, including in a "mix-and-match" manner.

Two human adenovirus-based vaccines are in use. Janssen's COVID-19 vaccine utilizes a replication-incompetent recombinant adenovirus type 26 as its vector. It has emergency use authorization for adults in the United States

who otherwise would not have access to an FDA-approved vaccine.[14] As with the mRNA vaccines, the Janssen vaccine contains the SARS-CoV-2 spike protein sequence. This vaccine's advantages include a single-dose immunization schedule and less-stringent requirements for refrigeration compared with mRNA-based vaccines. The Centers for Disease Control and Prevention and the FDA recommend the use of mRNA-based vaccines, when possible, over adenovirus-based vaccines because of the very small risk for VITT with the Janssen vaccine.[15]

The ChAdOx1 nCoV-19 vaccine from Oxford-AstraZeneca, generally known as the AstraZeneca vaccine, is not approved or authorized for use in the United States. More than 30 million doses have been administered in other regions, however, including Europe. ChAdOx1 is a replication-deficient simian adenovirus vector previously utilized in vaccine development, including in the influenza vaccine.[16] The AstraZeneca vaccine contains the full-length, codon-optimized spike protein of SARS-CoV-2 and a tissue plasminogen activator leader sequence (for enhanced expression and immunogenicity).[17] Anti-PF4 antibody formation in VITT related to the AstraZeneca vaccine has been attributed to manufacturing byproducts, not to the ChAdOx1 vector or the SARS-CoV-2 spike protein sequence.[18]

Additional vaccines are in use worldwide, and others are currently under development or have recently been approved for emergency use, such as the Novavax COVID-19 vaccine. This review focuses on the most widely available vaccines in the United States and on those with abundant safety data available.

Literature Search

On March 3, 2022, we searched PubMed with the following strategy: ((((covid[Title/Abstract]) OR (sars-cov-2[Title/Abstract])) AND (vaccine[Title/Abstract])) AND (thrombocytopenia[Title/Abstract])). Each result abstract was reviewed to verify that it included information on incident thrombocytopenia, ITP, or follow-up of patients with preexisting ITP. The reference lists of review articles were reviewed for any cohort or population-based studies that may have been missed in the initial PubMed search. Abstracts from the 2021 American Society of Hematology annual meeting were reviewed for unpublished reports. Two additional references published beyond the search date were incorporated based on relevance.

Incident ITP After SARS-CoV-2 Vaccines

Case reports abound in the literature describing new ITP in patients who had received either mRNA-based or adenovirus-based SARS-CoV-2 vaccines (reviewed by Al-Ali and colleagues[19]). However, only population-based studies can provide evidence for causality between a vaccine and ITP and assess the magnitude of risk for events that are too rare to detect in clinical trials. The best evidence available comes from case-controlled and self-controlled case series analyses. The self-controlled case series is an epidemiologic study design that has gained popularity in vaccine safety studies. This methodology utilizes self-controlled cases to derive associations between transient exposures and acute events.[20] In other words, the same population serves as cases and controls: persons are "controls" before they are exposed to a transient factor (eg, vaccination), and the incidence of an acute event (eg, thrombocytopenia) is measured. Then, the incidence of the same acute event is measured after vaccination. Statistical modeling accounts for the transient exposure and self-controlled characteristics. This study design is significantly more efficient and less costly than cohort studies and delivers similarly robust information.

Simpson and colleagues estimated that 11 new cases of ITP occurred per 1 million AstraZeneca vaccine doses in a study that included half the population of Scotland.[21] Patients presented most often between days 7 and 27 after vaccination. However, when the analysis was performed as a self-controlled case series, the cases of ITP that could be attributable to the vaccine were nearly halved from the initial estimate, decreasing from 11 to 6 cases of ITP per million doses administered (Table 2). The excess risk for ITP was confined to adults between the ages of 40 and 49 years. Three deaths occurred in both vaccinated and unvaccinated persons. The causes of death were reportedly unrelated to ITP. A study of similar design conducted in England also pointed to an excess risk for ITP among more than 19 million people who received the AstraZeneca vaccine.[22] Close to 1500 persons were admitted for thrombocytopenia (not restricted to ITP). The thrombocytopenia incidence rate ratio (IRR) was approximately 20% to 35% higher in that group between 8 and 28 days after vaccination compared with before vaccination (highest IRR, 1.33; noted 8-14 days from vaccination). However, the absolute risk was still quite small. This study added a fascinating perspective: among unvaccinated persons who tested positive for SARS-CoV-2 by polymerase chain reaction, the IRR for thrombocytopenia was as high as 75 on the day of COVID-19 diagnosis. These well-designed population-based studies suggest a causative link between the AstraZeneca vaccine and incident ITP but establish a low incidence rate for this complication. Of importance, they also help add perspective to the risk for ITP relative to the benefits of preventing severe COVID-19.

Additional retrospective population-based cohort studies show similar findings. Utilizing data from the National Health Service and other nationwide sources,

Andrews and colleagues[23] reported 11 admissions for "thrombocytopenia" attributable to the AstraZeneca vaccine per 1 million doses. Thrombocytopenia was most frequently noted 4 to 27 days from vaccine administration among persons ages 40 to 64 years old; the risk period extended beyond 28 days among individuals ages 15 to 39 years, although there is no clear biological rationale to support such findings. Pottegård and colleagues[24] reported on any thrombocytopenia/coagulation disorders among all people from Norway and Denmark who received the AstraZeneca vaccine between February 9 and March 11, 2021, a denominator of approximately 290,000 individuals. The incidence rate of ITP in those populations was 0.07 and 0.06 per 1000 person-years, respectively. It was impossible to conclude if these rates of new ITP cases was significantly different from the expected rate, given the rare number of events. On the other hand, the study demonstrates that ITP is still a rare event, and the absolute risk of vaccination is likely very low. Most importantly, there was a significantly lower risk for death among vaccinated individuals (standardized morbidity ratio, 0.34 [95% CI, 0.19-0.57]).

Vaccine adverse events monitoring systems offer additional clinical information on incident ITP after COVID-19 vaccination, although there are limitations related to the voluntary nature of reporting and to establishing a precise denominator. The Paul Ehrlich Institute in Germany compiles and reports data on vaccine safety for the Pfizer, Moderna, AstraZeneca, and Janssen products. Kowarz and colleagues[25] analyzed the data from the December 23, 2021 report, and identified the following ITP incidence rate per million doses: 2.6 for Moderna, 3.3 for Pfizer, 6.6 for Janssen, and 21.2 for AstraZeneca. Moulis and colleagues reviewed data from the French Pharmacovigilance Network.[26] Again, the AstraZeneca vaccine presented the highest risk for de novo or relapsed ITP (6.12 [95% CI, 4.63-8.04] per 1 million doses). Two cases of intracranial hemorrhage were identified in this cohort: an 84-year-old woman with an asymptomatic, 5-mm frontal intraparenchymal bleed and a 63-year-old man with a history of chronic lymphocytic leukemia and hypertension who was admitted to the hospital with a spontaneous intraparenchymal hemorrhage and subsequently developed ITP while hospitalized, leading to the fatal aggravation of the intracranial bleed.

Regarding mRNA vaccines from Pfizer and Moderna, Lee and colleagues[27,28] and Welsh and colleagues[29] performed similar reviews of the United States' Vaccine Adverse Event Reporting System (VAERS), with consistent findings. The estimated incidence rate for ITP after the Pfizer and Moderna vaccines combined was 0.8 per million doses (~1.6 per million people),[29] which is thought to be within the expected incidence rate for ITP in the general population.[27] An in-depth review of cases demonstrated that most patients respond to standard corticosteroids with or without intravenous immunoglobulin. Thrombopoietin receptor agonists and well-established but almost-forgotten therapies, such as vincristine, can be helpful in more-refractory cases.[28] The caveat to these studies is that VITT was not yet described when most of the cases were entered into VAERS, and some of those patients did present with thrombosis, which confounds the results as we cannot discriminate ITP from VITT in every case.

Battegay and colleagues[30] reviewed the World Health Organization's global vaccine adverse reaction database (VigiBase) and identified 199 cases, including terms referring to the Pfizer vaccine and ITP, among more than 26 million reports. Okada and colleagues[31] reviewed the Japanese adverse event reporting system for thrombocytopenia and hemorrhages following the Pfizer vaccine. They noted a small number of reports on isolated thrombocytopenia, but 8.8% of the reports included intracranial hemorrhage. However, similar outcomes were assessed in the sizable case-control series in England and Scotland, with no excess risk attributable to the Pfizer vaccine. These cohort studies utilized data from national health systems and therefore did not depend on voluntary reporting.

The precise mechanism by which the AstraZeneca vaccine formulation could cause ITP has not been established. One could hypothesize that some of these patients are on the VITT spectrum, and some guidelines recommend testing patients with thrombocytopenia for anti–platelet factor 4 (PF4) antibodies even in the absence of thrombosis.[32] Experiments in mice demonstrated that intravascular—but not intramuscular—injection of ChAdOx1 nCoV-19 generates adenovirus-platelet aggregates, which elicit a B cell–mediated immune response.[33] This immune reaction may give origin to anti-PF4 and other antiplatelet antibodies. Consistent with that hypothesis, anti-glycoprotein antibodies were found in 8 of 27 patients with confirmed ChAdOx1 nCoV-19–related VITT.[33] These data suggest that accidental intravascular injection of ChAdOx1 nCoV-19 could trigger antiplatelet antibodies in VITT and vaccine-induced ITP. It is unclear, however, if this phenomenon is limited to the AstraZeneca vaccine or if it could occur with other adenovirus-based products. It is also unclear how often accidental intravascular injection occurs.

Alternatively, Kowarz and colleagues[25] have suggested that adenovirus-based vaccines may generate a splicing variant of the spike protein, which could engage endothelial cells' angiotensin-converting enzyme 2 receptors and cause systemic inflammation, as observed with SARS-CoV-2. Adenovirus-based vaccines are subjected to splicing because their transcription happens in the nucleus, whereas transcription of mRNA-based vaccines

Table 2. Findings of Main Studies in Incident ITP and Exacerbation of ITP Following SARS-CoV-2 Vaccination

Author	Setting	Design	Main Finding
Simpson et al[21]	Scotland	Nationwide cohort study, self-controlled case series	The AstraZeneca vaccine was associated with an excess of 6 cases of ITP per million doses administered in adults aged 40-49 y.
Hippisley-Cox et al[22]	England	Nationwide cohort study, self-controlled case series	Thrombocytopenia IRR (including but not limited to ITP) was 20%-35% higher between 8-28 days post-vaccination vs pre-vaccination. In nonvaccinated persons who tested positive for SARS-CoV-2, the thrombocytopenia IRR was 75.
Lee et al[28]	United States and 1 center in the United Kingdom	Multicenter cohort study	ITP exacerbation in 17%-20% of patients. All patients who received medical therapy responded to rescue treatment.
Woolley et al[36]	United Kingdom	Single-center cohort study	14 patients with ITP relapse and 3 patients with new ITP after vaccination. 10 patients responded to treatment; 88% reported bruising or bleeding.
Visser et al[38]	The Netherlands	Multicenter cohort study	ITP exacerbation (as defined by Lee et al[28]) in 14% of patients; 2.2% incidence of bleeding.
Crickx et al[39]	France	Multicenter cohort study	3 out of 92 patients developed ITP exacerbation (platelet count $<30 \times 10^9$/L) attributable to SARS-CoV-2 vaccination. Bleeding incidence of 3.2%.

IRR, incidence rate ratio; ITP, immune thrombocytopenia; y, years.

happens in the cytoplasm. It remains to be established if the link between the AstraZeneca vaccine and ITP is the spike protein antigen or another vaccine component, what mechanisms may be at play in generating an antiplatelet immune response, and if similar phenomena happen with other adenovirus-based vaccines, such as the Janssen vaccine.

Newly diagnosed ITP following COVID-19 vaccination has been reported after both adenovirus- and mRNA-based vaccines. However, carefully designed epidemiologic studies have demonstrated that only the AstraZeneca vaccine may be causally linked to incident ITP. According to the best available estimates, the excess risk for ITP is on the order of 6 cases per million doses.[21] Though the Janssen vaccine has been associated with VITT, there is no robust evidence for a causal relationship with ITP. Ongoing assessment of vaccine safety is of utmost importance to the public. In this context, serious complications from incident ITP may be prevented with prompt recognition and implementation of recommended management strategies.

SARS-CoV-2 Vaccine Safety in Persons With Preexisting ITP

Patients with a history of ITP were particularly alarmed by the possible association between COVID-19 vaccines and severe thrombocytopenia, and so were their treating physicians. Patient and hematologist communities have assembled case series to explore the effect of COVID-19 vaccination in ITP patients (detailed below and highlighted in Table 2). Those studies have generally concluded that COVID-19 vaccination is safe among patients with ITP. Although transient thrombocytopenia exacerbations may occur, either they are self-limited, or patients can be promptly rescued with standard ITP therapies. When thrombocytopenia is not self-limited, it tends not to be long-lasting; the great majority of patients have their platelet counts back to baseline within 3 months, with or without treatment. Furthermore, serious bleeding events are rare.

Kuter[34] published the first series on ITP patients who were prospectively monitored for thrombocytopenia after receiving a SARS-CoV-2 vaccine. Defining ITP exacerbation as a 66% reduction in platelet count from the pre-vaccination count and new bleeding symptoms, 12% of the patients in that cohort were affected after receiving a vaccine dose (4 Pfizer, 1 Moderna, 1 Janssen). Five of the patients responded to corticosteroids with or without intravenous immunoglobulin, and only 1 patient required additional treatment with romiplostim (Nplate, Amgen) and rituximab. Fattizzo and colleagues[35] reported on the outcomes of 38 patients, of whom 1 received the AstraZeneca vaccine, 6 the Moderna vaccine, and the majority the Pfizer vaccine. Two patients developed ITP exacerbation in the setting of concurrent stressors (hip fracture, bronchitis exacerbation). In a study from the United Kingdom of 211 patients at their center, Woolley

and colleagues[36] reported a relapse of ITP in 14 patients and a new diagnosis of ITP in 3 patients. Most patients in that cohort received the Pfizer or AstraZeneca vaccines (53% and 27%, respectively), and 88% reported bruising or bleeding at the time of ITP relapse. Ten patients in this cohort achieved complete remission after treatment. Four patients were deemed refractory to treatment. However, there was no significant difference between their pre-vaccine and post-vaccine platelet counts (suggesting that ITP refractoriness preceded immunization). The Platelet Disorder Support Association—a US-based patient advocacy group—conducted an online survey among their community.[37] Among 267 respondents, 24 reported an absolute decrease in platelet counts of greater than 100 × 10^9/L after a vaccine dose, and 3 participants (1.1%) reported bleeding symptoms. These reports suggest that significant worsening of thrombocytopenia occurs but is infrequent and treatable. However, these studies did not identify any particular group of patients at increased risk.

Two large cohort studies sought to identify which patients with ITP were at risk for ITP exacerbations, with conflicting results. In the studies by Lee and colleagues[28] and Visser and colleagues,[38] ITP exacerbation was defined as any one of the following: a decline in platelet count of at least 50% from pre-vaccination levels, a post-vaccine count nadir below 30 × 10^9/L with an associated decrease of at least 20% from baseline, or use of additional therapy to rescue platelet counts at the discretion of the treating physician. This definition identifies more patients with less-severe thrombocytopenia or bleeding symptoms compared with the definition adopted by Kuter.[34] However, this broader definition captures both patients at risk for bleeding (ie, those with platelet counts <30 × 10^9/L) and patients whose worsening thrombocytopenia would encourage closer monitoring, with possibly more doctor visits/phlebotomies, and might lead to more anxiety.

Lee and colleagues[28] retrospectively evaluated 117 patients from tertiary ITP centers (all but 1 in the United States), of whom close to 90% received an mRNA-based vaccine. The incidence of ITP exacerbation was 17% after dose 1 and 20% after dose 2. Patients with more-refractory ITP—suggested by a history of splenectomy and more prior lines of therapy—were at the highest risk of experiencing ITP exacerbation. Preliminary results from patient association surveys in the United States and the United Kingdom confirmed the findings regarding higher-risk groups.[28,37]

Visser and colleagues[38] prospectively evaluated 218 ITP patients from 7 centers in the Netherlands. ITP exacerbation occurred in nearly 14% of patients, and only 2.2% reported a bleeding event. The researchers identified a baseline platelet count of less than 50 × 10^9/L and active use of ITP-directed therapy as risk factors for further exacerbation after vaccination. These characteristics may reflect the same phenomenon observed in the study by Lee and colleagues[28]: patients with more-refractory disease are at the highest risk. In the Dutch cohort, however, splenectomy was associated with a lower incidence of ITP exacerbation (as was older age).

Crickx and colleagues[39] reported a similar rate of bleeding symptoms (n=3) in a French cohort of 92 patients with ITP. They also noted that many patients who experienced ITP exacerbation had more-refractory preexisting ITP. Only 3 patients developed ITP exacerbation that was most likely attributable to SARS-CoV-2 vaccination. Although these studies may not provide a clear answer to which patients with ITP are at the highest risk for complications, all of the studies are reassuring in that severe adverse events related to worsened thrombocytopenia were rare.

Data on whether booster vaccines have similar or different effects on bleeding and platelet counts are not yet available. Future studies of booster vaccines are required to further inform us about their effects on platelets.

Conclusion

In response to the global COVID-19 crisis, public and private initiatives produced the SARS-CoV-2 vaccines faster than any vaccines ever developed. SARS-CoV-2 vaccines have been vital in mitigating the pandemic—a scientific accomplishment to be celebrated. However, the development speed, along with societal and political factors, has contributed to hesitancy and distrust. The wealth of available data points to a very small risk for incident ITP with the AstraZeneca vaccine, below that reported with the widely used measles, mumps, and rubella (MMR) vaccine.[40] As with the MMR vaccine, the benefits of vaccination for SARS-CoV-2 vastly overcome the very minor risk attributable to ITP. Different demographic groups may be affected by other potential complications, such as the risk for myocarditis observed in young men after the Pfizer and Moderna vaccines.[41-44] The absolute risk for a severe adverse outcome is very small. Health care providers are tasked with assisting individuals in making well-informed decisions regarding their health. If the risk for ITP leads some away from receiving the AstraZeneca vaccine, alternative products with an even more favorable safety profile from that perspective are currently available or in development in many countries. Ongoing vaccine pharmacovigilance and clear communication will continue to be fundamental in the global effort to mitigate the impact of COVID-19. Development or worsening of ITP are so uncommon, and severe hemorrhagic outcomes are so rare, that anything related to ITP should not hold back SARS-CoV-2 vaccination.

Disclosures

Dr Beltrami-Moreira has no potential conflicts of interest to disclose. Dr Bussel has served as a consultant or advisor for Amgen, UCB, Novartis, Sobi, Rigel, Argenx, Janssen, AstraZeneca, Sanofi, and CSL Behring, and has served on the data and safety monitoring board of UCB and CSL Behring.

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