Experience of an Infectious Diseases (ID) Travel Medicine Clinic During a National Shortage of Yellow Fever Vaccine (YFV)

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BACKGROUND

In April 2017, Sanofi Pasteur (SP), the sole supplier of Yellow Fever Vaccine (YFV) in the US, announced that supplies of YFV would be temporarily unavailable in the US. In conjunction with the FDA, SP launched an Expanded Access IND Program (EAP), to allow importation of YFV produced in France (Stamaril) by Sanofi Pasteur. Approximately 250 sites in the US were chosen based on geography, volume, and other factors. Our clinic, located in Eastern PA, was selected as one of those sites.

OBJECTIVE

To review our clinic's experience with the Stamaril EAP and to evaluate tolerance/ adverse effects in our practice.

METHODS

Our travel clinic is a medium-sized clinic that is embedded within a 14 Physician ID practice. We performed a 17-month review of Stamaril usage at our clinic.

RESULTS

Our physicians had to complete SP training, CITI (research ethics and compliance) training, and our own internal training before being able to prescribe Stamaril. Through 4/30/19, our clinic has administered 1,129 Stamaril doses, of which 844 were administered in 2018. Clinic visit volumes increased from 718 unique visits in 2017 to 1,402 in 2018 (95% increase). "Stamaril only" visits were 333 (24%) of total travel visits for 2018. Traveler's came from multiple states outside our catchment area. We documented 3 serious adverse events (SAE) whether or not considered related to the vaccine. One was a CDC confirmed case of Yellow Fever vaccine-associated neurotrophic disease (YEL-AND) in a 70-year-old male (fully recovered), another was new-onset generalized seizures (not confirmed as YEL-AND, fully recovered) in a 55-year-old male. The third was a Brighton Level 1 for diagnostic criteria and probable case for vaccine causality of Viscerotrophic disease (VTD) in a 65-year-old male (recovering). To accommodate increased volumes, we added 1 physician, and 1 Physician Assistant-Certified (PAC) to our travel rotations – 2 more providers are in training. We held 8 evening sessions to accommodate larger groups in need of YFV.

CONCLUSION

Participation in the Stamaril EAP program greatly increased our travel clinic volumes resulting in a need to add providers and extra hours to absorb demand. There were 3 serious adverse events (0.26%): 1 of which was confirmed to be YEL-AND and one probable for VTD for vaccine causality.

TRAVEL CLINIC STAFFING IMPACT

- Additional physician and PA-C providers were added/trained to absorb demand
- Required training included CITI training, Sanofi Pasteur Stamaril training, and Division travel provider onboarding (mentoring-based).
- For 2018, we held 8 evening clinic sessions (Up to 12 travelers per session).

TRAVEL CLINIC VISIT VOLUMES

- Participation in the Stamaril EAP program greatly increased our travel clinic visit volumes from 718 (2017) to 1,402 (2018) to projected 1,512 (2019) (See table 1+ 2)
  - Our Travel Clinic visit volumes continue to increase
  - Travel Visits to ID Visit ratio continues to rise
  - Stamaril only visits numbered 604 since implementation

ADVERSE EVENTS

- There were three Serious Adverse Events (All hospitalizations) for an SAE rate of 0.26% (through April 30,2019)
  - One of which was confirmed to be YEL-AND, one probable YEL-AVD*, and one seizure (unknown relationship).

    **Clinical criteria confounded by positive Clostridium difficile PCR in stool (patient felt to be colonized).*
  - All three patients were hospitalized and all three have been discharged.
  - Two are fully recovered and the most recent patient (YEL-AVD) continues to recover.
  - No other adverse events were encountered which were deemed to be vaccine related based on ID physician's clinical judgment.

TABLE 1: TRAVEL CLINIC VOLUME IMPACT

Year	Travel Visits (% increase from prior year)	Stamaril Only Visits (% increase from prior year)	Travel/ID visit Ratio (Percentage)
2017 (pre-Stamaril)	718 (N/A)	5 (N/A)	(N/A)
2018 (All Stamaril)	1402 (95%)	333 (N/A)	1459/4903 (30%)
2019 (Thru April 30)	504 (8%*)	266 (239%*)	504/1301 (39%*)
Total	(N/A)	604	(N/A)

**Estimated percentage extrapolated from 4 months of data to full calendar year.*

TABLE 2: STAMARIL DOSES GIVEN

Year	Doses
2017 (11/29-12/31)	16
2018 (1/1-12/31)	847
2019 (1/1-4/30)	266
Total	1,129

TABLE 3: STAFFING CHANGES

	2017	2018	2019 (Partial)
Physician	8	9 + trainee	9 + trainee
PA-C	1	2+ 2 trainees	3 + trainee
Nursing	6	6*	6
Evening Group sessions	0	8	0

** Additional shifts added for nursing staff.*

TABLE 4: SAE CASE REPORTS

Age/Sex	Onset Diagnosis	Symptoms/Lab data	Outcome
Case 1 70 Male	2/10/18 Confirmed YEL-AND	Admitted with fever, Headache and ataxia, 15 days after vaccination. LP with 146 WBC and 60 Protein. CSF: PCR-/IgM+	Fully recovered – no sequalae
Case 2 55 Male	4/23/18 New onset seizure – not confirmed as YEL- AND	Admitted with 2 generalized seizures within 2 weeks of YFV CSF: No pleocytosis, Protein 77. MRI Neg YFV PCR/IgM/PRNT all neg	Fully recovered – Brief course of anti-seizure medication
Case 3 65 Male	4/7/19 Probable YEL-AVD (Brighton Classification)[2]	Admitted with fever, malaise, diarrhea, AKI, Thrombocytopenia (Platelet nadir=64,000), increased LFTs (T bilirubin peak=2.0). Blood YFV 17D PCR + day 5 (2-3 log10 pfu/ml). PCR negative (day 14) C-diff + PCR	Creatinine peak of 8.2 with decrease to 6.9 at discharge. Discharged and recovering

SUMMARY

A nation-wide shortage of US produced yellow fever vaccine starting in 2017 has greatly changed our travel practice outpatient volumes – nearly doubling over one year. This has greatly changed the dynamics of our practice. Volumes continue to rise relative to general ID visits.

Staffing and ultimately our business plan for the future will continue to evolve as the EAP continues or ends. Based on our experience, travel clinics will need to find ways to plan and implement rapid changes in staffing plans for future vaccine shortages.

SAEs tended to occur in older travelers (mean age 64) and were seen only in males. Our numbers of SAE (3=0.26%) were numerically higher than previously published rates.[1,4] The reasons for this are not known but might be in part due to chance with relatively low visit volumes of a single travel clinic.

Enhanced safety surveillance may also have played a role in higher SAE rates, owing to the increased vigilance required of an IRB-approved EAP. Our observations agree with SP and FDA's ongoing assessment of all adverse events, including SAEs for this EAP, continued SP and FDA review is appropriate. All clinics involved in future EAP will need to carefully monitor patient adverse events and rapidly report any significant events in accordance with the EAP guidelines and IRB requirements.

DEFINITIONS

1. SAE: Serious Adverse Event: Any Stamaril recipient who was hospitalized, died, or had serious continued health problem whether or not considered related to the vaccine (6-week window).
2. YEL-AND: Yellow Fever Vaccine Associated Neurologic Disease
3. YEL-AVD: Yellow Fever Vaccine Associated Viscerotrophic Disease
4. VTD: Viscerotrophic Disease, by Brighton Classification
5. SP: Sanofi Pasteur
6. YFV: Yellow Fever Vaccine

TWO MAJOR WORKING GROUP SYSTEMS FOR CLASSIFICATION OF SERIOUS YFV REACTIONS

CDC definition of a Yellow Fever Adverse Reactions[1]

YEL-AND: includes Level 1,2 *clinical criteria* for ascertainment and assignment to Suspect, Probable, and Definite case definitions for YFV-AND based on virologic data (including YF 17D PCR in CSF/Serum, CSF IgM assay, PRNT assay.

YEL-AAD-CNS or YEL-AAD-PNS: categories for Yellow Fever Vaccine Associated Autoimmune Disease with CNS involvement.

YEL-AVD: Includes Level 1,2 clinical criteria for case ascertainment and assignment to Suspect, Probable, and Definite case definitions for YEL-AVD based on Liver dysfunction, 17-D virus PCR in serum, tissue, or detection of YF virus antigen by IHC in tissue.

BRIGHTON CLASSIFICATION FOR YEL-AVD

Developed in conjunction with WHO to define Yellow Fever Viscerotrophic Disease (VTD)[2]

Includes Case Definitions with Major and Minor criteria with thresholds and assignment to Vaccine-associated causality as Suspect, Probable, and Definite based on 17-D virus by PCR in blood, tissue histology, and also isolation of virus from tissue by IHC or PCR.

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