Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Salk A. et al. (2013) Ischemic colitis with type I interferons used in the treatment of hepatitis C and multiple sclerosis: an evaluation from the food and drug administration adverse event reporting system and review of the literature. *Annals of Pharmacotherapy*, 47(4):537-542.
Date of Review:	March 2, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other: multiple sclerosis, ischemic colitis** **Level:** **Group** ☒ **Individual** ☐ **Other:** **Target Population: HCV and multiple sclerosis patients** **Setting: Health care setting/Clinic** ☒ **Home** ☐ **Other:** **Country of Origin: United States** **Language:** **English** ☒ **French** ☐ **Other:**

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☐	☐	☒	Literature review; Examine the adverse events to characterize the association between type I interferon and ischemic colitis in patients with HCV and multiple sclerosis through the use of published reports and the FDA Adverse Event Reporting System
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☐	☒	☐	
Effectiveness	☐	☒	☐	

The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☐	☒	☐	
Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Analysis of 2,562,390 adverse events reported in the FDA Adverse Event Reporting System (AERS)
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☒	☐	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Methodology and data sources were described clearly
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	AERS is a publicly available database
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Annals of Pharmacotherapy*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☐	☒	☐	Purchase or subscription require for view at http://aop.sagepub.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
How is the best practice/intervention funded? ***Please got to Comments section***	☐	☒	☐	Study not funded

Other relevant information: _____	☐	☐	☐	- type I interferons may be initiating factors or cofactors in the development of ischemic colitis in patients with HCV and multiple sclerosis who are treated with the drugs

Ischemic Colitis with Type I Interferons Used in the Treatment of Hepatitis C and Multiple Sclerosis: An Evaluation from the Food and Drug Administration Adverse Event Reporting System and Review of the Literature

Allison Salk, Derrick J Stobaugh, Parakkal Deepak, Eli D Ehrenpreis

OBJECTIVE: To better characterize the association between type I interferons and ischemic colitis (IC) in patients with the hepatitis C virus (HCV) and multiple sclerosis (MS), by analyzing reports submitted to the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) and the published literature.

DATA SOURCES: A total of 2,562,390 reports of adverse events between January 2003 and June 2011 were downloaded from the FDA AERS. A literature review was performed on PubMed (January 1966-August 2012) using the MeSH terms interferon or interferon alfa or interferon beta and ischemic colitis separated by the Boolean operator "and" between the first 3 terms and the last term. Additional literature was identified by conducting a hand search of the reference list of the published literature identified in the initial search.

STUDY SELECTION AND DATA EXTRACTION: Cases were restricted to those with an indication of HCV or MS, a primary suspect drug of a type I interferon, and a reaction of IC. Full-length reports were requested and organized by type of interferon, age, sex, concomitant drugs, and comorbidities. The Naranjo probability scale was used to define cases as definite, probable, possible, or doubtful drug-induced adverse events.

DATA SYNTHESIS: Type I interferons, including interferon alfa (IFN-α) and interferon beta (IFN-β), are approved for the treatment of HCV and MS. IFN-α has been shown to induce IC, but a relationship between type I interferons and IC has not been clarified in the medical literature. Fifty-six primary suspect reports of type I interferons associated with IC in patients with HCV or MS were identified from the FDA AERS. Seventeen cases were reported with IFN-α and 39 cases were reported with IFN-β. The majority of the cases were in females (80%) and those between the ages of 50 and 65 years (52%). The Naranjo probability scale identified 13 probable and 4 possible cases of IFN-α–induced IC, and 19 probable and 20 possible cases of IFN-β–induced IC. In the literature, 11 cases of IFN-α–induced IC were reported, while there were no reports with IFN-β.

CONCLUSIONS: Our study suggests a possible association between treatment with type I interferons and the development of IC. Further research to determine the mechanism of this association is warranted.

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Interferons are pleiotropic cytokines with important immunomodulatory, antiviral, antiangiogenic, antiproliferative, and antitumor functions.[1] There are 2 major groups of interferons, type I and type II. Type I interferons are structurally related, share a common receptor (type I interferon receptor), and play an important role in immunity and autoimmunity. They are related to the pathogenesis of autoimmune conditions, and this autoimmune effect has been utilized in several medications. Specifically, type I interferons initiate cellular reactions that result in a host-protective antiviral response. Type I interferons include interferon alfa (IFN-α), approved by the Food and Drug Administration (FDA) for the treatment of the hepatitis C virus (HCV), and interferon beta (IFN-β), approved for multiple sclerosis (MS).[2]

There are 11 type I interferon medications available, including IFN-α-2a (Roferon-A), IFN-α-2b (Intron-A), IFN-α-n3 (Alferon-N), peginterferon alfa-2b (PegIn-

Author information provided at end of text.

tron), interferon alfacon-1 (Infergen), peginterferon alfa-2a (Pegasys), peginterferon alfa-2a and ribavirin (Peginterferon), IFN-β-1a (Avonex, Rebif), and IFN-β-1b (Betaseron, Extavia).[3-6] Common adverse effects of these medications include flulike symptoms and fatigue. Type I interferons have also been shown to rarely alter a patient's blood flow and lead to hypotension.[7]

Ischemic colitis (IC) is not a known adverse effect of all type I interferons; hypotension is an adverse effect and a common cause of IC. As the most common form of intestinal ischemia, IC results from a decrease in blood flow to the colon that causes inflammation.[8] IC may present with varying severity, but is most often characterized by abdominal pain, diarrhea, and hematochezia. A variety of medical conditions including sepsis, heart disease, and vasculitis predispose a patient to the development of IC. In addition, a number of medications can cause IC. Almost 50 drugs and drug classes have a known association with IC, including nonsteroidal antiinflammatory drugs (NSAIDs),[9] alosetron,[10] oral contraceptives,[11] triptans,[12] and pseudoephedrine.[13] These medications can cause IC through local vasospastic effect, systemic hypotension, vasculitis, thrombotic lesion induction, increased intracolonic pressure, and other undetermined mechanisms.[9] IC is a serious drug-induced condition, as untreated cases can result in bowel infarction, necrosis, and, in rare cases, death.[8] In published case reports, IFN-α has been suspected to induce IC, with an average time of onset of 20.1 weeks.[14] The incidence of IC with IFN-α varies between 0.2% and 14.3%,[15-17] while the incidence rate of IC with IFN-β is unknown. However, an association between type I interferons and IC has not been evaluated using a pharmacovigilance database.

Our aim was to better characterize the association of type I interferons with IC in HCV and MS patients by examining adverse event reports submitted to the FDA Adverse Event Reporting System (AERS), as well as published reports.

Data Sources

The AERS is a publicly available database based on voluntary reporting for postmarketing surveillance of all FDA-approved drugs. There are a total of 2,562,390 reports of adverse events between January 2003 and June 2011, which were downloaded and analyzed using SPSS 20. We found reports with an indication of "hepatitis C" or "multiple sclerosis" for all approved type I interferons (Roferon-A, Intron-A, Alferon-N, PegIntron, Infergen, Pegasys, Peginterferon, Avonex, Rebif, Betaseron, and Extavia) using both trade and generic names. As only "ischaemic colitis" is indicative of IC in the Medical Dictionary for Regulatory Activities, it was the only term used in the reaction column. Index cases were further limited to those listed as primary suspect drug role for one of the type I interferons.

We requested full-length reports of all relevant cases through the Freedom of Information Act. After reviewing the cases to establish authenticity, duplicate cases were eliminated. During this review, cases were defined as definite, probable, possible, or doubtful for causing the drug-induced adverse event per the Naranjo probability scale.[18] Cases defined as doubtful on the Naranjo probability scale with more likely causes for IC, such as sepsis or coronary artery disease, were eliminated from analysis. The cases were further organized by type of interferon medication, age, sex, concomitant drugs, and significant medical comorbidities.

A review of the literature was performed on August 9, 2012, to analyze published literature regarding type I interferon–associated IC. A PubMed search (January 1966-August 2012) was performed using the MeSH terms interferon or interferon alpha or interferon beta and ischemic colitis separated by the Boolean operator "and" between the first 3 terms and the last term. Additional literature was identified by conducting a hand search of the reference list of the published literature identified in the initial search.

Results

BASIC CHARACTERISTICS

A total of 69 primary suspect cases with type I interferons were initially identified in HCV and MS patients. Thirteen cases were eliminated from analysis because of more likely causes for IC: 4 patients also had sepsis, 3 had coronary artery disease, 2 had chronic constipation, 1 had congestive heart failure, 1 had recent surgery for rectal prolapse, 1 had chronic IC, and 1 had a procoagulant disorder (factor VIII clotting disorder). Among the 56 primary suspect reports without other likely causes (Table 1), 17 were in patients taking IFN-α and 39 were in patients taking IFN-β. Twenty-six patients did not have any significant comorbidities or concomitant medications that have an increased association with IC.

IFN-α

After applying the Naranjo probability scale,[18] 17 of the cases were either probable or possible, with 13 of the 17 IFN-α cases being defined as probable drug-induced events. Trade names in Table 2 were identified as primary suspect IFN-α medications for the event of drug-induced IC. The majority of the cases were in males (65%). Three patients were of an unknown age, with most (64%) between 50 and 70 years. Evidence of a colonoscopy, biopsy, or other documented medical confirmation for IC was present in 14 cases. On follow-up reports, 12 patients recovered, 3 did not recover, and information was unavailable for 2 of the reports.

In the literature review, there were 9 references identified, although 1 was eliminated due to the patients being on interleukin-2 as well as IFN-α.[14-17,19-23] We identified 11 cases of IFN-α–induced IC reported in patients with HCV. The cases included had a temporal relationship in which the medication was administered before the event of IC and the patient had no other conditions or medications that were a more likely cause. The majority of the cases were in males (7/11) and those older than 50 years (7/11). One patient had hypertension and 5 patients were concomitantly receiving ribavirin. Six of the patients did not have any significant comorbidities or concomitant medications that could increase the risk of IC. All of the patients recovered.[14-16,19-23]

IFN-β

Trade names in Table 2 were identified as primary suspect IFN-β medications. Nineteen of the 39 IFN-β cases were defined as probable cases of interferon-induced IC per the Naranjo probability scale. All of the probable cases were in females. Although 1 patient was of an unknown age, the majority of patients with information provided were between the ages of 50 and 70 years (11/18; 61%). Evidence of a colonoscopy, biopsy, or other documented medical confirmation for IC was present in 10 cases. Significant comorbidities and risk factors for IC were present in 3 patients with hypertension. Two patients were on NSAIDs and 1 patient was on NSAIDs and estrogen (Table 1), both concomitant medications that may increase the risk of IC.[9,11] Follow-up reports revealed that 16 patients recovered and 3 patients did not.

While nineteen cases were identified as probable, the other 20 cases were classified as possible IFN-β–induced IC according to the Naranjo probability scale. All of the cases were in females and the majority of patients (13/20) were between the ages of 50 and 70 years. Documented medical confirmation was recorded in 9 cases. Four patients had hypertension and 1 had dehydration (Table 1). Nine patients were on concomitant medications, including angiotensin-converting enzyme inhibitors, β-blockers, estrogen, NSAIDs, natalizumab, sumatriptan, olmesartan, and amlodipine. Nine patients had no significant comorbidities or concomitant medications that could increase the risk of IC. Thirteen patients recovered, while 3 did not, 1 patient died, and information was unavailable for 3 of the reports.

COMPARISON OF THE GROUPS

The median age was similar between patients taking IFN-α and those taking IFN-β (51 and 56 years, respectively). All of the IFN-β cases were in females, while 35% of IFN-α cases were in females. The rate of known recovery from IC for patients taking IFN-α (70.6%) was similar to the rate for those taking IFN-β (74.4%). There are 11 published case reports of IFN-α–induced IC in HCV patients compared to none published with interferon-β in MS patients.

Table 1. Case Characteristics by the Type of Interferon Medication Reported

Characteristic	IFN-α (n = 17)	IFN-β (n = 39)
Male, n	11	0
Age (years), median (range)	51 (37-70)	56 (26-73)
Dose (IU), median (range)	120 (3-180); 6 cases unknown	30 (8.8-44); 5 cases unknown
Time of onset (days), median (range)	90 (8-333); 4 cases unknown	922 (10-4509); 10 cases unknown
Cases with no significant comorbidities or concomitant medication, n	2	24
Cases with concomitant medication, n	Ribavirin, 12	NSAID, 3; estrogen, 2; ACE inhibitor, β-blocker, estrogen, and olmesartan, 2; natalizumab, 1; estrogen and NSAID, 1; estrogen, sumatriptan, and NSAID, 1; ACE inhibitor and NSAID, 1; β-blocker and amlodipine, 1
Cases with significant comorbidities, n	Hypertension, 4	Hypertension, 7; dehydration, 1
Outcome, n	Recovered, 12; ongoing, 3; unknown, 2	Recovered, 29; ongoing, 6; death,1; unknown, 3

ACE = angiotensin-converting enzyme; IFN-α = interferon alfa; IFN-β = interferon beta; NSAID = nonsteroidal antiinflammatory drug.

Discussion

In our analysis of the FDA AERS, we identified 56 cases of IC associated with an exposure to type I interferons. Of those with a probable cause of drug-induced IC per the Naranjo probability scale, most patients recovered shortly after hospitalization. Patients taking IFN-α and IFN-β had similar recovery rates (70.6% and 74.4%, respectively). The literature regarding drug-induced IC in general, as well as specifically interferon-induced IC, report that most patients recover shortly after diagnosis, consistent with the results of our study.[9,14] Our data are also consistent with the available literature on drug-induced IC, as most cases were nongangrenous, resolved shortly after diagnosis, and developed at a younger age than typical in IC patients.

Older individuals have a higher risk of developing IC, with over 90% of IC cases described in the literature diagnosed in patients over the age of 60 years.[24] Our study findings differ, in that only 19.6% of cases were in patients older than 60 years, with 19 of 56 patients (34%) being 50 years and younger. Considering the age distribution of typical IC patients, these results suggest that type I interferon–induced IC targets a younger age group, although this may be the result of interferon use being more common in younger individuals. It has been reported that physicians are hesitant to prescribe interferon to older patients because of the possibility of adverse events, which may influence our findings.[25]

Sex differences were noted for the different type I interferons. HCV is equally common in males and females; however, females have a lower probability of disease progression. In light of this, women with HCV have the tendency to defer treatment or take medications less potent than interferons, compared to males.[26] These reasons could account for the fact that our study presented almost twice as many cases reported in men compared to women developing IC after receiving IFN-α for HCV. Conversely, IC occurring in patients treated with IFN-β was more common in females. This is consistent with an overall female predominance in MS seen in clinical epidemiology studies.[27] Since exogenous estrogen use is also a risk factor for IC, the risk for IC may be further accentuated in females.[28] The sex comparison is only an observation, as there is no denominator or process to control for confounders, but the data support the literature.

IFN-α has been suspected to induce IC in 11 published case reports.[14] Possible mechanisms of action have been proposed, including gastrointestinal vasculitis secondary to the immune-modulating effects of interferon; vasculitis is a known cause of IC. Interferons have also been suspected to cause a direct vasospastic effect that leads to a decrease in blood flow, possibly resulting in a lack of blood flow to the colon.[14] Although rare, hypotension is a known adverse effect of interferon treatment in addition to being a known risk factor for IC.[29] It is foreseeable that one or more of these factors could have led to IC with the use of either type I interferon.

Both HCV and MS have other treatment options that do not include interferons. The following FDA-approved medications could alternatively be used to treat MS: glatiramer acetate, mitoxantrone, and fingolimod.[3] For HCV patients, ribavirin and immunomodulators may be used.[26] Physicians treating patients with heart disease, diabetes, and other conditions that are associated with an increased risk of IC should take into account the adverse effects of interferon versus other alternative therapies when choosing the treatment regimen for those disorders.

The AERS is a voluntary reporting system with submissions from physicians, pharmacists, consumers, health care professionals, and attorneys; thus, underreporting is likely. Also, there is a possibility of misdiagnosis, as there are published reports of worsening ulcerative colitis with interferon treatment in HCV, and several of the cases did not provide confirmation of IC diagnosis with colonoscopy or biopsy.[30] We attempted to compensate for misdiagnoses by reviewing the full-length reports. Furthermore, our study does not prove causality, but instead suggests a correlation that complements the existing published literature available on this topic. Furthermore, the incidence of this adverse event also cannot be calculated from the AERS. There is no published information on the rates of IC in HCV and MS populations. Finally, vasculitis may develop in HCV patients independent of the medication used in treatment, and vasculitis is a risk factor for IC.[31]

In conclusion, we present 13 probable and 4 possible cases of IFN-α–associated IC as well as 19 probable and 20 possible cases of IFN-β–associated IC. Our findings suggest that type I interferons may be initiating factors or cofactors in the development of IC in patients with HCV and MS who are treated with these drugs. The AERS cannot assess the true incidence of IC caused by type I interferons, nor can it establish causation because of its structure as a voluntary reporting system. Further research to determine the mechanism of this adverse event is warranted. Nonetheless, this identified signal should alert clinicians treating patients with type I interferons that IC is a potential risk of these treatments.

Table 2. Trade Names of Type I Interferons Reported with Ischemic Colitis

Interferon alfa	Interferon beta
Intron-A	Avonex
PegIntron	Rebif
Pegasys	
Peginterferon	
Infergen	

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Conflict of interest: Authors reported none

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EXTRACTO

Colitis Isquémica con Interferonas Tipo I Usadas en el Tratamiento de Hepatitis C y Esclerosis Múltiple: Una Evaluación del Sistema de Reporte de Eventos Adversos de la Administración de Drogas y Alimentos y Revisión de la Literatura

A Salk, DJ Stobaugh, P Deepak, ED Ehrenpreis

Ann Pharmacother 2013;47:537-42.

OBJETIVO: Las interferonas Tipo I (IFNs), incluyendo IFN-α y IFN-β, están aprobadas para el tratamiento de hepatitis C y esclerosis múltiple. La IFN-α ha demostrado inducir colitis isquémica, pero no se ha aclarado en la literatura médica una relación entre IFN Tipo I y colitis isquémica. Buscamos caracterizar mejor la asociación entre IFNs Tipo I y colitis isquémica en pacientes de hepatitis C y pacientes de esclerosis múltiple, mediante el análisis de reportes sometidos al Sistema de Reporte de Eventos Adversos de la Administración de Alimentos y Drogas y de la literatura publicada.

FUENTES DE DATOS: Un total de 2,562,390 reportes de eventos adversos entre enero 1966 y agosto 2012 fueron bajados del Sistema de Reporte de Eventos Adversos de la Administración de Alimentos y Drogas.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Los casos fueron restringidos a aquellos con una indicación de hepatitis C, o esclerosis múltiple, una droga "sospechosa primaria" de IFN Tipo I, y una reacción de colitis isquémica. Los reportes completos fueron solicitados y organizados por tipo de IFN, edad, género, drogas concomitantes, y comorbilidades médicas. La Escala Naranjo reveló los casos definitivos, probables, posibles o dudosos de eventos adversos inducidos por drogas. Se llevó a cabo una revisión de la literatura en PubMed.

SÍNTESIS DE DATOS: Cincuenta y seis reportes de casos sospechosos de IFNs Tipo I asociados con colitis isquémica en pacientes con hepatitis C, o esclerosis múltiple, fueron identificados. Diecisiete casos fueron reportados con IFN-α y 39 casos fueron reportados con IFN-β. La mayoría de los casos fueron en mujeres (80%) y en aquellos con edades entre 50 y 65 (52%). La Escala Naranjo reveló 13 casos probables y 4 posibles de colitis isquémica inducida por IFN-α. La escala reveló 19 casos probables y 20 posibles de colitis isquémica inducida por IFN-β. Once casos de colitis isquémica inducida por IFN-α fueron reportados en la literatura, mientras que no hubo reportes con IFN-β.

CONCLUSIONES: Nuestro estudio sugiere una posible asociación entre el tratamiento con interferonas Tipo I y el desarrollo de colitis isquémica. Se justifica ulterior investigación para determinar el mecanismo de esta asociación.

Traducido por Ana E Vélez

RÉSUMÉ

Colite Ischémique Associée aux Interférons de Type I Utilisés Pour le Traitement de l'Hépatite C et de la Sclérose en Plaques: Une Évaluation à Partir du Système de Surveillance de la FDA des États-Unis d'Amérique et de la Littérature Médicale

A Salk, DJ Stobaugh, P Deepak, ED Ehrenpreis

Ann Pharmacother 2013;47:537-42.

OBJECTIF: Les interférons (IFN) de type I, en particulier les IFN-α et les IFN-β, sont approuvés pour le traitement de l'hépatite C (VHC) et de la sclérose en plaques (SEP). Il a été démontré que les IFN-α peuvent produire une colite ischémique (CI), mais la relation entre les IFN de type I et la CI n'est pas bien établie dans la littérature médicale. L'objectif de cette analyse était de caractériser l'association entre les IFN de type I et la CI chez les patients porteurs du VHC et les patients souffrant de SEP. Pour ce faire, les déclarations soumises au système de surveillance des réactions indésirables de la FDA des États-Unis d'Amérique ont été analysées et la littérature médicale a été revue.

PROVENANCE DES DONNÉES: Les cas d'IC où un IFN de type I était prioritairement suspecté chez des patients atteints de VHC ou de SEP ont été identifiés à partir des 2,562,390 déclarations de réactions indésirables enregistrées entre janvier 1966 et août 2012 dans le système de surveillance de la FDA des États-Unis d'Amérique. Les rapports complets ont été obtenus et analysés selon le type d'IFN, l'âge et le genre des patients, la présence de médicaments concomitants, la comorbidité, et le lien de causalité évalué par l'algorithme d'imputabilité de Naranjo. Une revue de la littérature médicale indexée à la banque de données PubMed a aussi été effectuée.

RÉSUMÉ: La recherche du système de surveillance de la FDA des États-Unis d'Amérique a identifié 56 cas où un IFN de type I était principalement suspecté comme agent causal d'une CI chez des patients atteints de VHC ou de SEP. Pour 17 de ces cas, il s'agissait d'un IFN-α alors qu'un IFN-β était impliqué dans 39 cas. La majorité des cas ont été rapportés chez des femmes (80%) et chez les individus âgés de 50 à 65 ans (52%). L'algorithme d'imputabilité de Naranjo suggère un lien de causalité probable pour 13 des 17 cas avec IFN-α et possible pour les 4 autres. Dans les cas impliquant l'IFN-β, l'algorithme suggère un lien probable dans 19 des 39 cas et possible pour les 20 autres. La recherche de la littérature médicale a identifié 11 cas avec l'IFN-α et aucun avec l'IFN-β.

CONCLUSIONS: Notre analyse suggère une association possible entre les IFN de type I et la CI. Des études supplémentaires pour déterminer les mécanismes pouvant expliquer cette association seront nécessaires.

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