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Assessment of Efficacy, Safety, and Appropriate Use of Filgrastim and Pegfilgrastim as Primary Prophylaxis for Neutropenia/Febrile Neutropenia in Chemotherapy Patients - A Prospective Observational Study

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ABSTRACT

Prophylaxis with recombinant G-CSF is recommended to prevent febrile neutropenia. Even though the G-CSF use was reported to reduce the incidence of neutropenic events, its use must outweigh the serious adverse events. Due to the substantial reduction in the cost of growth factors, there has been extensive use even with chemotherapy regimens having a lower risk of neutropenia (< 20%). So the purpose of our study is to assess the efficacy, safety & appropriateness of filgrastim and pegfilgrastim when given as primary prophylaxis for neutropenia/FN in patients undergoing chemotherapy. We conducted a prospective observational study for 6 months at a single institution in Salem, Tamilnadu. A total of 46 patients were included. The primary outcome measure of efficacy is in the terms of the Absolute neutrophil count, Total WBC count, and body temperature. And the adverse effects associated with the G-CSF'S are assessed via the direct interview with the patient using the checklist and graded by using the CTCAE. The appropriateness was assessed using the NCCN guidelines. 17.3 % of patients developed FN/Neutropenia, despite being given the G-CSF prophylaxis. The most commonly observed AE was mild-moderate bone pain which constitutes about 26.3 % in the pegfilgrastim group and 22.2% in the Filgrastim group. 55.09% of the cost of the G-CSF total doses contributed by appropriate use and 44.90% of the cost of the total doses accounted by inappropriate use of G-CSF which implies the additional treatment-related costs. The FN incidence was higher among the patients who received Filgrastim than Pegfilgrastim prophylaxis. The incidence of bone pain was higher among the patients who had not been given the prophylaxis for the bone pain. In the patients with inappropriate use of G-CSF, the mean number of avoidable doses per patient was 2.45 (±1.66).

INTRODUCTION:

According to the Indian Society of Medical and Pediatric Oncology (ISMPO) Guidelines, Febrile neutropenia is defined as the single oral temperature of 38.3°C (101.4°F) or 38.0°C (101°F) over 1 hour with less than 500 neutrophils/ mm^3 or less than 1,000 neutrophils/mm^3 with a predicted decline to 500/mm^3 over the next 48 hours.

The incidence of FN in the USA is estimated at 60,294 per year including 7.83 cases per 1000 cancer patients. Moreover, the incidence rises to 43.3 cases per 1000 in individuals that are suffering from the hematological malignant tumors[1]. In a nationwide prospective cohort study, first-cycle febrile neutropenia occurred in 6% of adults with solid tumors being treated with myelosuppressive chemotherapy[2]. The investigation in India by Jacob et al. revealed that FN episodes occurred more frequently in patients with solid tumors (57%) than those suffering from hematological malignancies[1].

Since FN in cancer patients is usually a direct consequence of chemotherapy, an evaluation of risk factors associated with FN is necessary before any attempt to prevent the occurrence of the condition[3].FN may adversely affect the treatment outcomes as it may lead to treatment interruption, dose reductions, and even termination of chemotherapy. The cost incurred due to the hospitalization and the use of antibiotics is also significant[4]. Hence, it is important to take necessary precautions to prevent the occurrence of FN by the use of primary prophylaxis with granulocyte colony-stimulating factor (G-CSF). Prophylaxis with recombinant granulocyte-colony stimulating factor (G-CSF) is recommended to prevent febrile neutropenia and associated secondary events such as infections. Over the decades, the current use of G-CSF prophylaxis provides substantial benefit, reducing cases of febrile neutropenia (FN) by 3.3 million and cases of chemotherapy reduced dose intensity (RDI) less than 85% (RDI<85%) by 354,000, resulting in $96 billion in social value (SV)[5].

A relatively common and sometimes severe, a patient-reported adverse event is mild to moderate bone pain, which develops in 10 to 30% of patients who receive these agents. Non-narcotic analgesics usually control these symptoms[6,7]. Bone pain is of considerable concern to patients, because the pain may be severe. Patients might give up treatment due to severe bone pain which in turn puts the patients at the risk of neutropenia and its associated complications. The utilization of less intensive regimens as a strategy to reduce the risk of febrile neutropenia may negatively impact the treatment outcomes, particularly in curative settings. The administration of G-CSF or pegylated G-CSF after chemotherapy is rarely

associated with acute myeloid leukemia or the myelodysplastic syndrome[8] and rare cases of splenic rupture have also been reported with G-CSF's[7].

Even though the use of G-CSF was reported to reduce the incidence of neutropenic events, its use must outweigh the serious adverse events.

The Practice has changed dramatically in India of late. Growth factor usage has increased exponentially and is becoming cheaper day by day. Due to the substantial reduction in the cost of growth factors, there has been extensive use even with chemotherapy regimens having a lower risk of neutropenia (< 20%). Lastly, unique to our country, due to challenging logistics, e.g. difficult terrain, inaccessible medical facilities, and inability to reach the hospital within 24 hours of the onset of fever many International guidelines are flouted and India-centric innovative measures are needed[9]. So, the purpose of our study is to assess the efficacy and safety of filgrastim and pegfilgrastim when given as primary prophylaxis for neutropenia/FN in patients undergoing chemotherapy and also to assess the appropriate use of the G-CSF as primary prophylaxis with the guidelines.

MATERIALS AND METHODS:

We conducted a prospective observational study for 6 months at a single institution in Salem, Tamilnadu. The primary objectives of our study were to assess the efficacy and safety of filgrastim and pegfilgrastim as primary prophylaxis in the chemotherapy patients and then to evaluate the appropriateness of prescribing G-CSF prophylaxis with guidelines and secondary objectives was to assess the prophylaxis given for G-CSF associated bone pain and to evaluate the cost incurred with the inappropriate prescribing of G-CSF's. The study was specifically designed with inclusion and exclusion criteria, such that the patients undergoing chemotherapy with the G-CSF as primary prophylaxis alone were taken into the study.

The outcome measures for efficacy were when patients come for the review of the next cycle of their chemotherapy, the primary outcome measure of efficacy is in the terms of the Absolute neutrophil count, Total WBC count, and body temperature. And the adverse effects associated with the G-CSF'S are assessed via the direct interview with the patient using the checklist and graded by using the Common Terminology Criteria for the Adverse Events version 5.0 [CTCAE]. By using the following table, we have assessed the appropriateness of the prescription of G-CSF as primary prophylaxis in our study.

Appropriate use:

RISK ASSESSMENT OF FEBRILE NEUTROPENIA	OVERALL FN RISK
✓ Chemotherapy regimen FN risk > 20% (NCCN guidelines) especially in Chemotherapy naive patients ✓ Dose-dense chemotherapy	HIGH > 20%
✓ Chemotherapy regimen FN risk 10-20% (NCCN guidelines) ✓ Curative intent ✓ ≥ 1 Patient-specific Risk factors	INTERMEDIATE RISK (10-20%)
✓ Receiving chemotherapy based on at least one study supporting the use of G-CSF in those settings	CONSIDERED APPROPRIATE

Inappropriate use:

RISK ASSESSMENT OF FEBRILE NEUTROPENIA	OVERALL FN RISK
✓ Chemotherapy regimen with 10-20% FN risk (NCCN guidelines) without any patient-based risk factors. ✓ Palliative chemotherapy	INTERMEDIATE RISK (10-20%)
✓ Chemotherapy regimens with <10 % FN risk	LOW RISK (< 10%)

This study was conducted according to the ethical requirements stated in the Declaration of Helsinki. All participants received information before giving their informed consent. They were also informed that only the researchers would have access to the data and the results will be used for publication purposes and their identity will be kept confidential. The ethical clearance for our study was approved by the Institutional ethical committee and Hospital authority.

STATISTICAL ANALYSIS:

We have used descriptive statistics in our study, for the patient characteristics. Continuous variables were summarized as mean and standard deviation and categorical variables were

summarized as several patients with percentages. The interpretations for the categorical variables were performed using the Chi-square test and the level of significance was set at less than or equal to 0.05.

RESULTS:

A total of 46 patients were included in our study and were observed. The median age of the population in the study was 56 (SD 11.52) and the majority of the patients were from 40-59 years which is 52.1%. There was a greater Female preponderance which is 58.6 %, followed by the male proportion which is 41.3 %. In our study, the breast cancer patients proportion was higher which is 21.73%, which is followed by Non-Hodgkin's lymphoma which is 15.21%. The majority of the patients were undergoing chemotherapy of the Curative intent which comprised 60.86% and 39.13 % of the palliative intent. A greater proportion of patients were in the category of the high risk which constitutes about 32.6%, which is followed by 30.43% of low-risk regimens. The baseline characteristics of the population in the study are given in the below table.

Table No. 1: Baseline Characteristics

Characteristics	Number Of Patients	Percentage (%)
AGE(Years)		
MEAN	56.34	
SD	11.52	
GENDER		
FEMALE	27	58.6
MALE	19	41.3
TUMOR TYPE		
BREAST CANCER	10	21.73
NHL	7	15.21..
PANCREATIC CANCER	5	10.86
STOMACH CANCER	4	8.69
HL	3	6.52
LUNG CANCER	3	6.52
UTERINE CANCER	2	4.34
OVARIAN CANCER	2	4.34
COLON CANCER	2	4.34

OTHERS	8	17.39
CHEMOTHERAPY INTENT		
Curative	28	40.86
Palliative	18	39.13
FN RISK LEVELS		
HR	15	32.6
IM Risk with 1 Risk Factor	11	23.91
IM Risk	6	13.06
LR	14	30.43
STAGE OF TUMOR		
NON METASTASES	14	30.43
METASTASES	32	69.56
CHEMOTHERAPY REGIMEN		
R-CHOP	6	13.04
TIP	1	2.17
FOLFIRINOX	5	10.86
FOLFOX	2	4.34
Dose dense ACT	7	15.21
AC followed by sequential T	1	2.17
Dose dense Doxorubicin	2	4.34
TCbH	1	2.17
Nab paclitaxel+carboplatin	2	4.34
Pemetrexed+carboplatin+Pembrolizumab	1	2.17
Pemetrexed+carboplatin	1	2.1
Pemetrexed+carboplatin+Bevacizumab	1	2.17
Paclitaxel+carboplatin	3	6.52
BeGEV	1	2.17
Procarbazine+Methotrexate+prednisolone	1	2.17
BR	3	6.52
Cisplatin+Etoposide	1	2.17
AVD	1	2.17
FLOT	3	6.52
Daunorubicin+Vincristine	1	2.17
Gemcitabine+Carboplatin	1	2.17
Gemcitabine+Docetaxel	1	2.17

Table No. 2: Patient Based Risk Factors Amplifying FN Risk

Factors amplifying FN risk	Number of patients	Percentage (%)
Age > 65 years	13	28.26%
Low-performance status (low karnofsky index/high ECOG score)	2	4.34%
Comorbidities including COPD, heart failure (NHYA III-IV), HIV infection, Autoimmune disease, marked renal impairment	2	4.34%
Significantly advanced, symptomatic tumor disease	20	43.47%
Prior chemotherapy	6	13.04%
Laboratory parameters including anemia, lymphocytopenia (< 700 Cells/µl), Hyperalbuminuria, hyperbilirubinemia	2	4.34%

INCIDENCE OF NEUTROPENIC EVENTS:

The efficacy of the G-CSF was assessed based on, whether the patients developed neutropenic events (NE) that is the development of neutropenia or febrile neutropenia at the next cycle review.

Table No. 3: Incidence of Neutropenic Events

Neutropenic events	Number of patients n (%)	Median Duration (Range)
Neutropenia without fever	1 (2.17)	1 (1)
Febrile neutropenia	7(15.21)	2 (1-3)

8 patients developed neutropenic events. 1 patient developed neutropenia without fever, with a median duration of 1 day and 7 patients developed Febrile neutropenia with a median duration of 2 days.

17.3 % of patients developed Febrile neutropenia/Neutropenia, despite being given the G-CSF prophylaxis, and among those, with Intermediate risk regimen based patients had a

higher incidence of FN which constituted about 6.52 % and then 4.34% of Intermediate risk regimen with 1 or more RF and Low-risk regimens and then 2.17% of patients developed FN/Neutropenia among the High-risk regimens.

And the common consequences of the FN/ Neutropenia incidence were the chemotherapy delay and in one case among the LR regimens, it leads to the chemotherapy dose reduction.

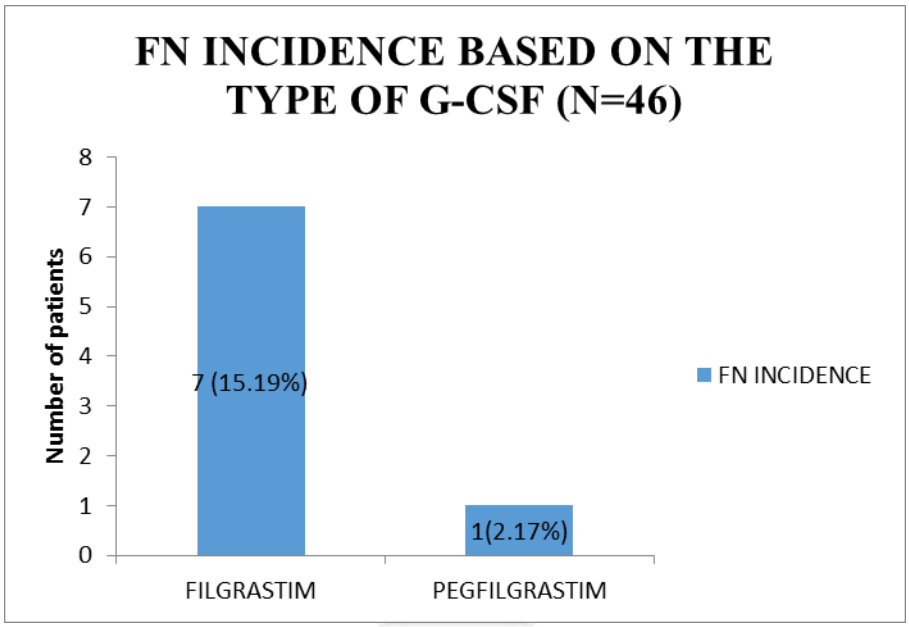

Figure No. 1: FN Incidence Based on GCSF Type

The FN incidence despite the G-CSF prophylaxis was higher among the patients who received Filgrastim than Pegfilgrastim prophylaxis (15.19% versus 2.17%). And the timing of the G-CSF administration was after 24 hours in both Filgrastim and Pegfilgrastim groups.

FN/NEUTROPENIA INCIDENCE ACCORDING TO THE CANCER TYPE AND CHEMOTHERAPY REGIMEN

The incidence of FN/Neutropenia despite the G-CSF prophylaxis was higher among the NHL Cancer patients (8.68%), receiving the R-CHOP regimen, as shown in the table below.

Table No. 4: FN/Neutropenia Incidence According To The Cancer Type And Chemotherapy Regimen

Cancer	Chemotherapy regimen	Number of patients developed FN/Neutropenia	Percentage (%)
Breast cancer	TcBH	1	2.17%
HL(Relapsed)	BeGEV	1	2.17%
NHL	R-CHOP	2	4.34%
NHL (DLBCL GCB)	R-CHOP	1	2.17%
Breast cancer	AC followed by sequential taxanes	1	2.17%
NHL (DLBCL)	R-CHOP	1	2.17%
Endometrial cancer	Nab.paclitaxel+carboplatin	1	2.17%

Table No. 5: Adverse Events According To The Pegfilgrastim And Filgrastim Encounters

Adverse event	CTCAE grading	Pegfilgrastim (N=19)		Filgrastim(N=27)	
		n	%	n	%
Neutropenia	Grade-2	-	-	1	3.70%
Febrile neutropenia	Grade-3	1	5.2%	6	22.2%
Extreme Fatigue	--	1	5.2%	2	7.40%
Mild bone pain	Grade-1	5	26.3%	6	22.2%
Severe bone pain	Grade-3	1	5.2%	-	-
Severe musculoskeletal pain	Grade-2	1	5.2%	-	-
Vomiting	--	-	-	2	7.40%
Leukocytosis	Grade-2	3	15.7%	1	3.70%
Thrombocytosis	Grade-1	-		1	3.70%
Thrombocytopenia	Grade-1	3	15.7%	-	-
Eosinophilia	Grade-1	1	5.2%	1	3.70%
Abdominal pain	--	-	-	1	3.70%
Constipation	--	-	-	1	3.70%
Prolonged QT	Grade-1	-	-	1	3.70%
ST-elevation	Grade-1	-	-	1	3.70%
Elevated AKP	Grade-2	1	5.2%	-	-
Anemia	Grade-2	-	-	2	7.40%
Elevated serum creatinine	Grade-2	-	-	2	7.40%
Neuropathy	Grade-2	-	-	1	3.70%

The most commonly observed AE was mild-moderate bone pain which constitutes about 26.3 % in the pegfilgrastim group and 22.2% among the Filgrastim group.

Table No. 6: Comparison Of Bone Pain In Prophylaxis Given Patients Versus Not Given Patients

Bone pain prophylaxis	Number of patients (N=46)	Percentage (%)	Bone pain incidence (N=13)	Percentage (%)
Given	29	63.04%	6	46.15%
Not given	17	36.95%	7	53.84%

The incidence of bone pain was higher among the patients who had not been prescribed the prophylaxis for the bone pain which accounted for 53.84% versus 46.15% for the prophylaxis given patients.

COMPARISON OF BONE PAIN INCIDENCE IN FILGRASTIM VS PEGFILGRASTIM ENCOUNTERS

The below table shows that the incidence of bone pain was higher among the Filgrastim prophylaxis patients (63.63%) versus 36.36% for the Pegfilgrastim prophylaxis.

Table No. 7: Incidence of the bone pain

Type of G-CSF	Bone pain incidence(N=11)	Percentage (%)	Consequences of the Bone pain
Pegfilgrastim	5	38.46%	1 case of severe BP leading to Hospitalization and from the next cycle, it was changed to Filgrastim
Filgrastim	8	61.53%	Nothing of serious consequence

COMPARISON OF COST OF G-CSF DOSES IN APPROPRIATE USE VERSUS INAPPROPRIATE USE

The cost of the G-CSF doses was compared between the appropriate use versus the inappropriate use. The appropriate use of G-CSF is considered as Chemotherapy regimens of High risk and IM risk with patient-based risk factors supported by the NCCN guidelines and the existing literature evidence and the prescription of G-CSF in chemotherapy regimens with

Intermediate risk and Low risk are considered as inappropriate use and the doses were considered as avoidable doses.

Table No. 8: Comparison of Cost of G-CSF Doses In Appropriate Use versus Inappropriate Use

Use of G-CSF	Total number of doses (N=103)	Total doses cost (in rupees)	Percentage cost (%)	Number of doses		Results		
				Mean	SD	df	$\chi 2$	p-value
Appropriate	59	1,04,680	55.09%	2.23	1.47	1	18.5	<0.0001**
Inappropriate	44	85,328	44.90%	2.45	1.66			

The above table shows that 55.09% of the cost of the G-CSF total doses contributed by appropriate use and 44.90% of the cost of the total doses accounted by inappropriate use of G-CSF. In the patients with inappropriate use of G-CSF, the mean number of avoidable doses per patient was 2.45 (SD 1.66).

THE SUBGROUP ANALYSIS OF THE LOW-RISK REGIMENS

We have further analyzed the possible reasons for the administration of G-CSF in the low-risk regimen patients through the chart review and patient interviews and calculated the total percentage of each conceivable reason.

These possible reasons were adopted from: NCCN guidelines suggests the consideration of the use of G-CSF in the low-risk regimens if the patient is receiving the Curative or adjuvant treatment and is at significant risk for serious medical consequences of FN and according to the ISMPO guidelines, Inaccessible medical facility and long distance to reach the hospital was adopted.

Table 9: Sub Group Analysis of The Low-Risk Regimens:

Conceivable reasons for the G-CSF administration in LR regimen	Number of patients (14)	Percentage (%)
Curative intent	5	35.71%
Relapse/Refractory	2	14.28%
Dose-dense chemotherapy	1	7.14%
Inaccessible medical facility	2	14.28%
Long-distance to reach the hospital	5	35.71%

The above table of sub-analysis shows that the Curative intent of the chemotherapy in the patients and long distance to reach the hospital, being the greatest possible reason for the administration of G-CSF among the patients with Low-risk regimens which accounted for 35.71% each and it is followed by the Inaccessible medical facility and relapsed/refractory cases account for 14.28% and dose-dense chemotherapy which accounted for 7.14%.

DISCUSSION:

The most common type of cancer was breast cancer, which is followed by NHL, Pancreatic cancer, and stomach cancer. This is complementary to the findings of a study[10] which revealed breast cancer and NHL as the most common type of cancer. In our study, significantly advanced/symptomatic tumor disease being the most common patient-based risk factor accounts for 43.47% in our study, which is followed by age > 65 years account for 28.26 %. But in contrast with our study, One study [11]concluded that prior chemotherapy, abnormal hepatic and renal function and Low WBC's being the most common patient-based risk factor for G-CSF administration.

FN incidence was higher among the Filgrastim group. In consistent with our study, one study[12] of network meta-analysis, in which evidence suggested that compared with placebo, most of the tested G-CSF drugs are not different in terms of efficacy and tolerability, except for Pegfilgrastim, which is more effective than Filgrastim in reducing FN.

In The Indian Society of Medical and Pediatric Oncology (ISMPO) guidelines, it has been mentioned that uniquely to our country, due to challenging logistics, e.g. difficult terrain, inaccessible medical facilities, and inability to reach the hospital within 24 hours of the onset

of fever many International guidelines are flouted and India centric innovative measures are needed. And consistent with this, we have also found in our study, that almost 35.7% of patients had to travel quite a distance to reach the hospital and 14.3% of patients had the inaccessible medical facility and that could explain the administration of G-CSF in those low-risk regimens cases.

CONCLUSION:

17.3 % (8 out of 46) patients developed Febrile neutropenia/Neutropenia, despite being given the G-CSF prophylaxis and the FN incidence was higher among the patients who received Filgrastim than Pegfilgrastim prophylaxis (15.19% versus 2.17%) and the FN/ Neutropenia incidence was higher among the NHL patients with R-CHOP regimen which accounted for 8.68%.

The most commonly observed AE was mild-moderate bone pain which constitutes about 26.3 % in the pegfilgrastim group and 22.2% in the Filgrastim group. The incidence of bone pain was higher among the patients who had not been given the prophylaxis for the bone pain which accounted for 53.84% versus 46.15% for the prophylaxis given patients.

The incidence of bone pain was higher among the Filgrastim prophylaxis patients (61.53%) versus 38.46% for the Pegfilgrastim prophylaxis. However, among the patients who were given the Pegfilgrastim prophylaxis, one patient had severe Bone pain which leads to Hospitalization, and from the next cycle, it was changed into Filgrastim prophylaxis.

55.09% of the cost of the G-CSF total doses contributed by appropriate use and 44.90% of the cost of the total doses accounted by inappropriate use of G-CSF which implies the additional treatment-related costs. In the patients with inappropriate use of G-CSF, the mean number of avoidable doses per patient was 2.45 (SD 1.66). And the subgroup analysis showed that the Curative intent of the chemotherapy in the patients and long distance to reach the hospital, being the greatest possible reason for the administration of G-CSF among the patients with Low-risk regimens.

LIMITATIONS:

The Sample size of our study was small due to the pandemic and some samples were excluded because the follow-up of the patients was not possible. Since it is an observational study, the patients in the study had different types of cancer and thus received varied chemo-

therapeutic regimens, hence further studies are pertinent to study the drug in a larger population about a particular regimen.

The greater efficacy of Pegfilgrastim in our study, which may be a result of underdosing of Filgrastim, since there was a difference in the duration (in terms of days) was given in routine practice. For some AE's in our study, the attribution of causality to a particular G-CSF was not possible.

FUTURE RECOMMENDATIONS:

Uniquely to our country India, transportation or difficulty in access to hospitals, being one of the main specific patient-related problems to be taken into the consideration, and also in some cases, it may warrant the use of G-CSF prophylaxis in patients who do not meet the guidelines criteria. So, these should be assessed on, case by case basis and it would be time-consuming, especially considering the case burden for the treating physician. So, an appropriate solution would be the clinical pharmacist in collaboration with the physician expertise to assess those patients and to determine the rationale and need for the use of G-CSF and to create an institution based reference which would be suitable for that geographic region which could significantly reduce the additional treatment-related costs.

In our study, 36.95% of patients had not been given prophylaxis for bone pain and since it is also of, considerable concern and in mindful of the fact of the potential dangers of chemotherapy delay and its consequences and polypharmacy, there is a clear lacuna in providing this care and the clinical pharmacist could fill in the gap by carefully assessing the risks and benefits when deciding the course of treatment for each patient.

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