



POST-MARKETING ACTIVE PHARMACOVIGILANCE IN A CENTRAL HOSPITAL



CP-076

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Background

Hospital settings are of great value in collecting pharmacovigilance data. ⁽¹⁾ Introduction of innovative drugs in hospital setting raises safety concerns, but allows the study of these drugs' safety profile in real life. Hospital Pharmacists may play an important role in these activities.

Among the various methods for carrying out Pharmacovigilance in hospitals, in parallel to the spontaneous reporting programs, we can name: epidemiological methods, intensive surveillance and voluntary reporting, or indirect methods ("alert" drugs' monitoring, allergies' monitoring, monitoring of clinically important drug interactions, among others) to identify adverse drug reactions and thus increase detection rates and notification from hospitals.⁽¹⁾

The Pharmacy Department of a central Hospital in Lisbon, Portugal, selected the intensive surveillance on the use of drugs, as its method since 2010. Since it is not possible to include all drugs in such intensive surveillance programs (active pharmacovigilance program), a prior selection is done at the time of drug's approval by the decision-making body of the institution on the basis of product characteristics, including potential toxicity and associated marketing time. Priority is given to the newer medicines which are intended to more serious diseases. After a period of intensive monitoring, the selected medicine passes into spontaneous reporting system.

Purpose

Assess the adverse drug reactions (ADRs) profile of 3 recently marketed drugs introduced in a central hospital.

Methods

As part of our active pharmacovigilance programme, a prospective, observational study was carried out on patients receiving fingolimod, telaprevir (TVR) or boceprevir (BOC), between January 2012 and September 2014.

To this purpose, clinical files were evaluated and interviews to patients or caregivers were carried out and registered as appointments. Encountered ADRs were analysed concerning age, sex, ADR category, and seriousness. Severe, unexpected, frequent, infrequent or rare ADRs were reported to the National Pharmacovigilance System (NPS).

Results (I)

A total of 41 patients were enrolled and a total of 253 ADRs were observed (Table 1).

Medicine	N Patients	Median Age	% MALE	% FEMALE	Total N Patients w/ ADRs	N of ADRs
Fingolimod	25	42	24	76	23	94
Boceprevir/Telaprevir regimens	16	49	63	37	14	159
Total	41	44	41	59	37	253

Table 1: Demographic data & n° ADR observed

About 28 reports regarding 173 ADRs were sent to NPS. As per the Naranjo causality assessment of ADRs to suspected medicines (Table 2) established:

- 90 ADRs with a possible causal relation;
- 53 ADRs with probable causal relation;
- 1 ADR with a definitive causal relation;

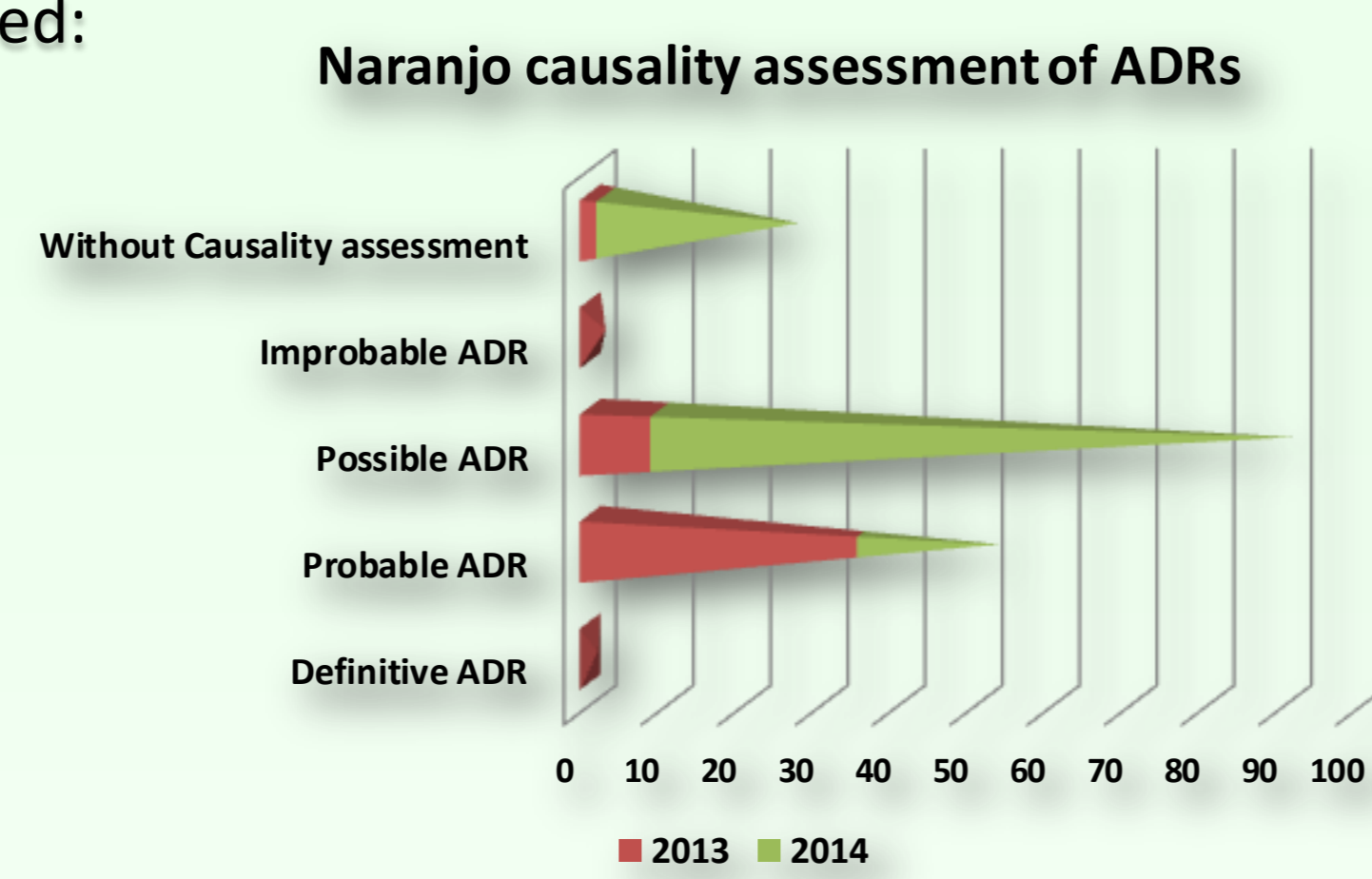


Table 2: Naranjo causality assessment of ADRs

The NPS response rate was 83%. ADRs categories were also analysed, with observance of:

- 16 unexpected ADRs;
- 8 infrequent ADRs;
- 3 rare ADRs.

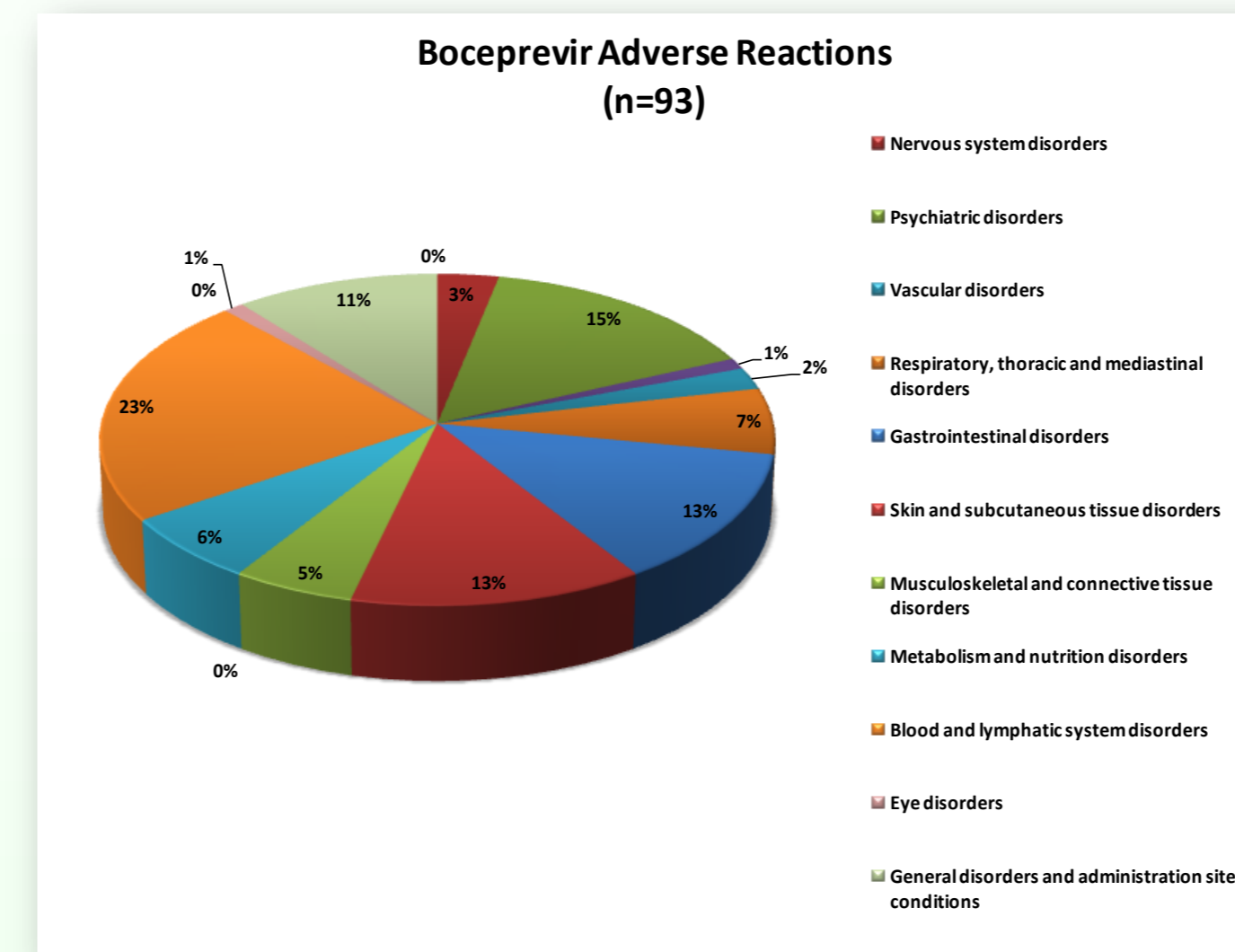
Severe ADRs occurred in 5%, and moderate ADRs in 16% of the cases. Therapeutic discontinuation was seen in all studied drugs.

Most frequently observed ADRs (n=159) in patients with BOC/TVR regimens were:

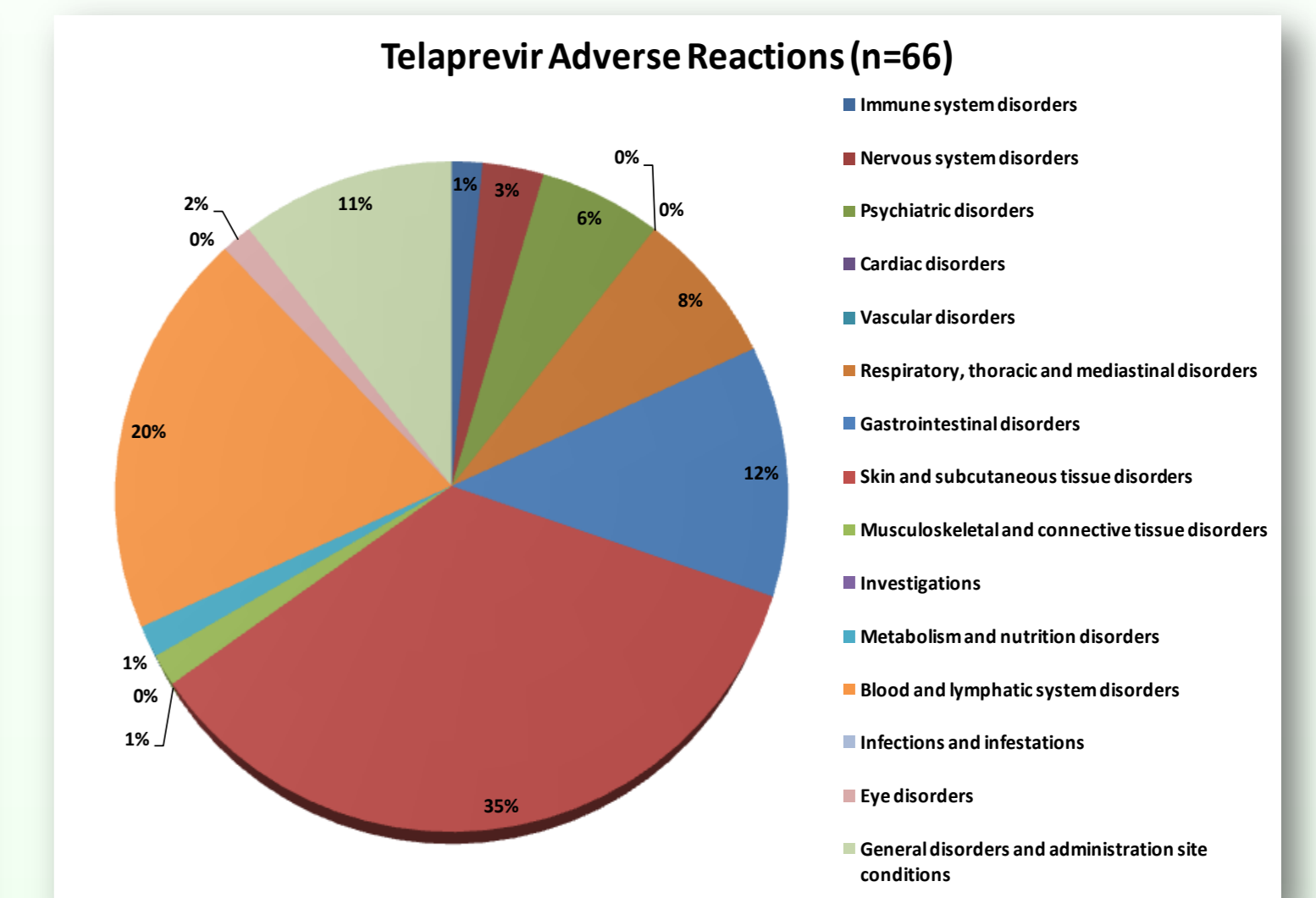
- Anaemia (70%), thrombocytopenia (78%), and pruritus (57%);
- Haemoglobin and platelets levels prior to therapy were evaluated and anaemia and thrombocytopenia was detected in 19% (n=3) and 31% (n=5) of the patients, respectively;
- Median nadir observed was 9.8 g/dL Haemoglobin (7.1 – 12.6 g/dL) and 86x10⁹ Platelets count (26-157x10⁹), respectively;
- Unexpected and uncommon ADRs were 5,7 and 3,8%, respectively;

Results (II)

Treatment emergent adverse reactions of BOC and TVR are summarized in Graph 1 and 2, according to MedDRA system organ class:



Graph 1: Boceprevir ADRs

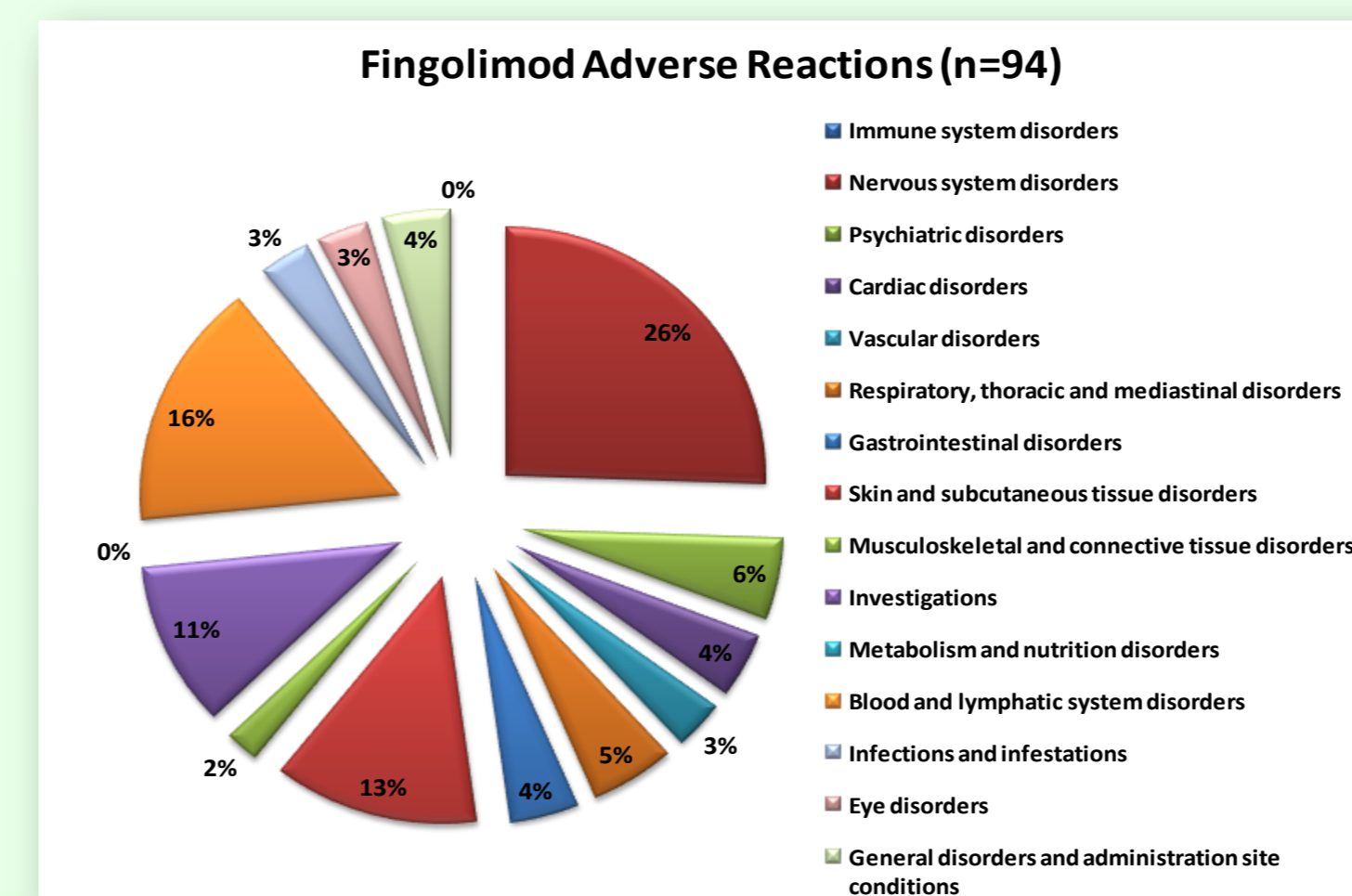


Graph 2: Telaprevir ADRs

Regarding fingolimod (n=94), most frequently observed ADRs in patients were:

- Lymphopenia (60%) and paresthesia (24%);
- initial dose ECG monitoring was performed in all patients, but symptomatic bradycardia was seen in only two cases, without therapeutic discontinuation;
- Unexpected and uncommon ADRs were 7,4 and 2,2%, respectively.

Fingolimod's treatment emergent adverse reactions, according to MedDRA system organ class, is summarized in Graph 3:



Graph 3: Fingolimod ADRs

Pharmacovigilance activities are shown in Table 3:

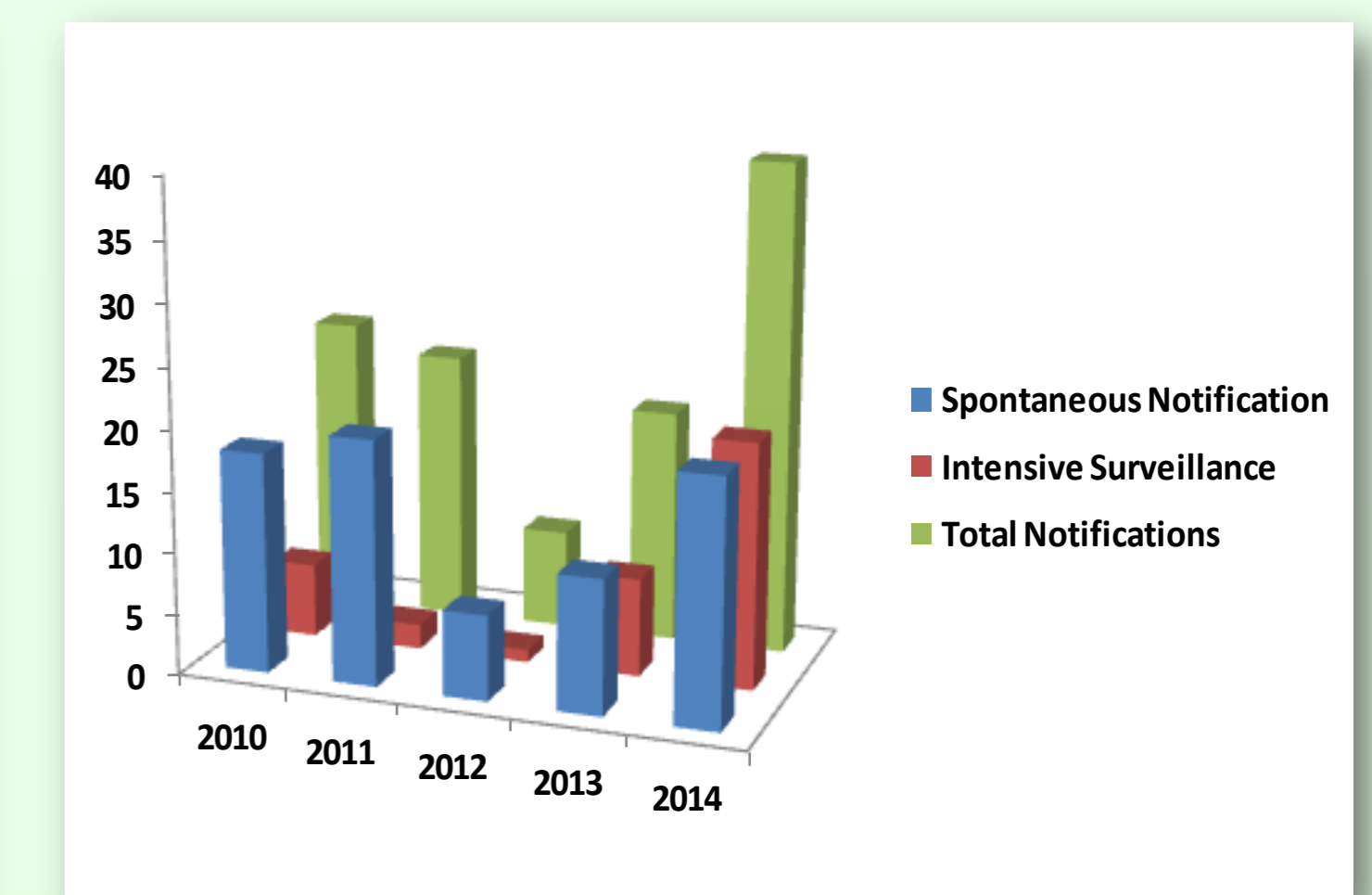


Table 3: Active Pharmacovigilance activities

In 2014, 50% of the notifications to NPS were data from the ongoing active pharmacovigilance program. A total of 113 appointments were made between 2010 to 2014.

Discussion/Conclusion

Fingolimod is used to reduce relapses and disability progression in relapsing forms of Multiple Sclerosis. Several screening studies and a first-dose observation period are recommended due to adverse effects observed in clinical trials. ^(2,3) Our observations allows us to affirm:

- First-dose observation period was performed in all patients and was uneventful in 23 patients (92%);
- Other screening studies were complied to a minor extent (baseline ophthalmologic evaluation and VZV serology evaluation or VZV vaccination).
- As expected ^(2,3), **nervous system disorders** (headache, paresthesia, and migraine), **reduction of circulating lymphocytes, and elevation of liver function tests** were commonly detected in our fingolimod-treated patients.
- According to the conducted interviews, **paresthesia** had a negative impact on daily activities;
- Skin disorders** (alopecia, pruritus, eczema) were relevant in our population (13% of fingolimod related ADRs) and perceived as important by our patients;
- From a cardiovascular standpoint, fingolimod was safe in our population, but tachycardia occurred in one patient, leading to therapeutic discontinuation;
- Discontinuation was also observed in another case, due to disease severity measures worsening;
- There were no severe or serious infections in this population.

BOC and TVR were the 1st direct-acting antiviral agents that directly impeded viral replication. Recently, 2nd line direct-acting antiviral agents have been approved. Triple therapy is associated with increased adverse events, and thus requires closer patient observation compared with the previous treatment.⁽⁴⁾ Additionally, BOC and TVR may induce HCV-resistant mutations, and clinical failure will eventually emerge.⁽⁵⁾ Our study allows us to state:

- Complete blood counts were obtained at pretreatment, and at Treatment Weeks 2, 4, 8, 12, as warranted ⁽⁶⁾;
- Other screening studies were complied to a minor extent (platelet count, serum albumin and International Normalized Ratio at baseline);
- As expected, **Blood and lymphatic system disorders and Skin disorders** were commonly detected in our BOC/TVR-treated patients;
- Frequency of **anaemia and thrombocytopenia** was higher than described in clinical trials. However, neutropenia, was reported less frequently than expected;^(5,6)
- Severe skin reactions were observed in two telaprevir-treated patients (including a rare event), leading to therapeutic discontinuation;⁽⁴⁾
- Psychiatric disorders** (Anxiety, depression, insomnia, irritability -15%) **were relevant in BOC treated-patients**, while less relevant in TVR treated patients;
- Gastrointestinal disorders** incidence was similar in both drugs (Diarrhoea, nausea, vomiting, dry mouth, dysgeusia – 12-13%);
- Therapeutic failure was detected in one BOC triple regimen treated patient.

Limitations to this study include: compliance data weren't assessed; Memory bias and record bias could play a significant role in our study.

Since its introduction in the hospital, the intensive surveillance of medicines allowed a quantitative and qualitative increment in pharmacovigilance activities. Adverse events were common in patients taking triple drug regimen for hepatitis C, while fingolimod was relatively well-tolerated, which is in line with international literature data. Frequency and severity of ADRs can be managed by laboratory's and clinical parameters' vigilance and instituting appropriate measures.

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