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Infliximab Paediatric Crohn's Disease Educational Plan

A European, Cross-Sectional, Multicentre Evaluation

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Abstract

Background: The infliximab (Remicade®; Schering-Plough, Kenilworth, NJ, USA) Risk Management Plan included the development, execution and tracking of an education programme directed towards prescribers of infliximab for patients with paediatric Crohn's disease (the Infliximab Paediatric Crohn's Disease Educational Plan). The programme content consisted of educational materials and communications aimed at educating prescribers on the risks associated with infliximab use.

Objective: To evaluate the effectiveness of the risk minimization plan.

Methods: Evaluation focused on two components: documentation of training of sponsors' personnel, and evaluation of awareness among prescribing physicians in European countries. Treating physicians, identified both independently of the sponsor (6 countries) and by the sponsor (24 countries), were surveyed using a structured questionnaire.

Results: Training of internal staff on the educational programme was performed and completed by every person designated an appropriate candidate for the programme in all European countries. The independent survey conducted in Germany, France, Italy, Spain, Sweden and the UK indicated that around 90% of the physicians were either paediatric gastroenterologists (57%) or paediatricians (33%). The great majority (96%) of the interviewed physicians were currently treating paediatric Crohn's disease, and most were currently using infliximab in their treatment of the disease. More specifically, 82% of gastroentrologists treating paediatric Crohn's disease were using infliximab; among paediatricians, the proportion was lower (42%).

Ninety-six percent of paediatric gastroenterologists or gastroenterologists declared themselves aware of the benefits and risks of using infliximab for the treatment of paediatric Crohn's disease; in comparison, fewer paediatricians (82%) declared themselves aware of these benefits and risks. The majority initially gained awareness through congresses and workshops, and at the time of the survey only 25% declared that they were made aware of the benefits and risks through the educational programme. However, the majority of physicians reported that they had been approached by the sponsor's personnel in France (98%), Italy (100%), Spain (83%) and Sweden (70%). In Germany and the UK this proportion was 42%.

Almost all physicians were aware of the need to perform tuberculosis (TB) and cancer screening prior to initiating therapy with infliximab, and to screen for hypersensitivity reactions before, during and after treatment. Ninety percent of the physicians were aware of the need to update immunization therapy before initiating therapy and, except in Italy (92% aware), around 50% of the physicians were aware of the need to provide patients with the infliximab Patient Alert Card.

In the other European countries where the survey took place among physicians identified by the sponsor, 99% of paediatric gastroenterologists and 90% of gastroenterologists or paediatricians declared themselves aware of the benefits and risks of using infliximab for the treatment of paediatric Crohn's disease, and all of them were aware of the risk of TB and opportunistic infections and the need to perform TB and cancer screening prior to initiating therapy with infliximab.

Conclusions: Overall, the results of the evaluation of the Infliximab Paediatric Crohn's Disease Educational Plan were satisfactory. The objective of education of internal personnel of the pharmaceutical companies distributing infliximab was completely achieved; over 90% of physicians reported being aware of the benefits and risks of infliximab for the treatment of paediatric Crohn's disease. Further work should be carried out across all countries to educate physicians on providing patients with the infliximab Patient Alert Card. In Germany and the UK in particular, where <50% of physicians reported having been approached by the sponsor's personnel, further work is needed to raise awareness of the educational programme.

Background

As part of the submission for approval of the anti-tumour necrosis factor (TNF)-α antibody infliximab (Remicade®) for use in patients with paediatric Crohn's disease,[1] the Marketing Authorization Holder (MAH) Centocor (Leiden, the Netherlands), and Schering-Plough (Kenilworth,

1 Variation II.75, adopted by the Committee for Medicinal Products for Human Use (CHMP) on 22 March 2007, with corresponding EU Commission Decision issued 30 May 2007.

NJ, USA), the local representative of the MAH in Europe, agreed to submit a Risk Management Plan (RMP).

A key consideration in the development of the RMP was that children may have an increased risk of developing infections in association with TNF-targeted treatment, and it is important for immunizations to be up-to-date and to prescreen all patients who are biological treatment candidates for both active and latent tuberculosis (TB) using adequate procedures. There is also a risk of acute administrative-related reactions and delayed hypersensitivity reactions, and the risk of lymphoma and other malignancies should be considered and discussed before the decision to treat with infliximab is made.[1-3]

The RMP included the development, execution and tracking of an additional education programme (the Infliximab Paediatric Crohn's Disease Educational Plan) directed towards prescribers of infliximab for patients with paediatric Crohn's disease. The objective of the educational plan is to promote the correct use of infliximab.

The use of educational activities is a well established means of promoting, preserving and restoring public health.[4] Systematic programme evaluation is an effective way of improving and monitoring public health actions using procedures that are useful, feasible, ethical and accurate.[5] The objective of this study was to evaluate the effectiveness of the Infliximab Paediatric Crohn's Disease Educational Plan in Europe.

Crohn's disease is characterized by patchy, transmural inflammation, which may affect any part of the gastrointestinal tract. The prevalence of Crohn's disease is higher in northern regions than in southern regions, and in Europe ranges from 213–214 cases per 100 000 persons in Sweden and the UK to 8.3–19.3 per 100 000 persons in Croatia and Spain.[6-20] In a systematic review of population-based cohorts of patients with Crohn's disease in North America, the prevalence of Crohn's disease in the US was estimated at 144.1 cases per 100 000 persons.[21]

Crohn's disease is most commonly diagnosed in late adolescence and early adulthood, but may occur in all age groups.[22,23] In a systematic review conducted in North America, the mean age at diagnosis ranged from 33.4 years to 45 years,[21] whereas the median age at diagnosis was 29.5 years.[24] Once considered rare in the paediatric population, Crohn's disease is being recognized with increasing frequency among children[25] and has become one of the most important chronic diseases affecting children and adolescents. In approximately 20–30% of all patients, Crohn's disease presents when patients are younger than 20 years of age. In these cases, the disease usually presents at between 12 and 16 years of age, but it has been detected in children as young as 7 years of age. In a recent study in Wisconsin, USA, the incidence of Crohn's disease in children was 4.56 per 100 000.[26]

In addition to the common gastrointestinal symptoms of diarrhoea, rectal bleeding and abdominal pain, children with Crohn's disease often experience growth failure, malnutrition, pubertal delay and bone demineralization. The unique problems encountered in the paediatric population necessitate a medical approach that promotes clinical improvement and reverses growth failure with minimal toxicity.

The objective of our study was to evaluate the Infliximab Paediatric Crohn's Disease Educational Plan by measuring the degree of training of internal (sponsor's) personnel on the content of the educational programme, and the awareness of physicians with regard to the safety concerns included in the infliximab RMP.

Methods

Overall Evaluation of the Infliximab Paediatric Crohn's Disease Educational Plan

The educational plan includes two distinct areas: education of the sponsor's personnel and education of relevant prescribers of infliximab (gastroenterologists, paediatric gastroenterologists), and other healthcare professionals such as nurses (see Appendix 1, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A28. This supplementary material contains a summary of the content of the educational material, the questionnaire used and the Patient Alert Card). The educational programme content

consists of educational materials and communications aimed at educating prescribers on the risks of the occurrence of lymphoma, TB, the potential for infusion reactions and opportunistic infections associated with infliximab, relative to other approved or commonly prescribed therapies.[1-3]

The study was a European, multicentre, cross-sectional evaluation of the effectiveness of the educational plan using questionnaires delivered to prescribers and the sponsor's personnel by different methods. The evaluation of the educational plan consisted of a three step process:

1. The creation of a tracking system to measure compliance with training on the educational programme by the sponsor.
2. In Germany, France, Italy, Spain, Sweden and the UK, independent research institutes and consultancies identified healthcare practitioners treating patients with paediatric Crohn's disease. These countries were selected because they represent the most populated countries within the EU and because of the feasibility of obtaining a sample of prescribers without involvement from the sponsor. A structured questionnaire was developed independently of the sponsor and used for evaluating the degree of awareness of prescribers on the risks included in the RMP (see Appendix 2, Supplemental Digital Content). The survey took place from July through to 15 September 2008 (figure 1).
3. In other European countries, including Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Croatia, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Malta, Norway, Holland, Portugal, Poland, Romania, Serbia, Slovenia and Slovakia, a list of targeted prescribers was created by the sponsor's sales force and medical staff (figure 1).

A survey among prescribers of infliximab was conducted to examine the comprehension of and to investigate penetration of the key educational messages included in the RMP. In Germany, France, Italy, Spain, Sweden and the UK, the independent research institutes and consultancies delivered and retrieved the questionnaires. In the other European countries the questionnaire was delivered to all targeted physicians personally by the sales force, marketing staff or medical liaison. Target physicians were those who treat paediatric Crohn's disease and have treated paediatric Crohn's disease patients with infliximab. The educational material and the questionnaire were developed in English and either submitted in the original language or translated to the local language depending on the assessment of English proficiency of the general prescribers by the sponsor. There was one slight difference between the questionnaires used in the two sets of countries. For the six main countries, questions 7 and 8 were combined into one.

Internal Evaluation of Sponsor's Staff

In all European countries (table I), a list of individuals, including the gastrointestinal sales force, employees from medical departments and marketing departments, and sales representatives who were deemed appropriate candidates to receive the educational programme was created. An e-mail tracking system to measure the reception of the education and the certification of awareness of each individual staff member of the MAH who received the training material was also created.

Evaluation of the Educational Plan in Germany, France, Italy, Spain, Sweden and the UK

Identification of Prescribers

Because different medical and cultural practices exist in each country, the methodology employed to contact and gather information from prescribers was adapted based on each country's specific practices. Given that at the start of the study it was not known whether there were going to be differences in accessing prescribers among countries, and that it was important to avoid over representation by a single country, the target was a maximum of 50–100 prescribers per country.

Germany

There is no official list of institutions that treat paediatric Crohn's disease patients in Germany. The first step in collecting contact information

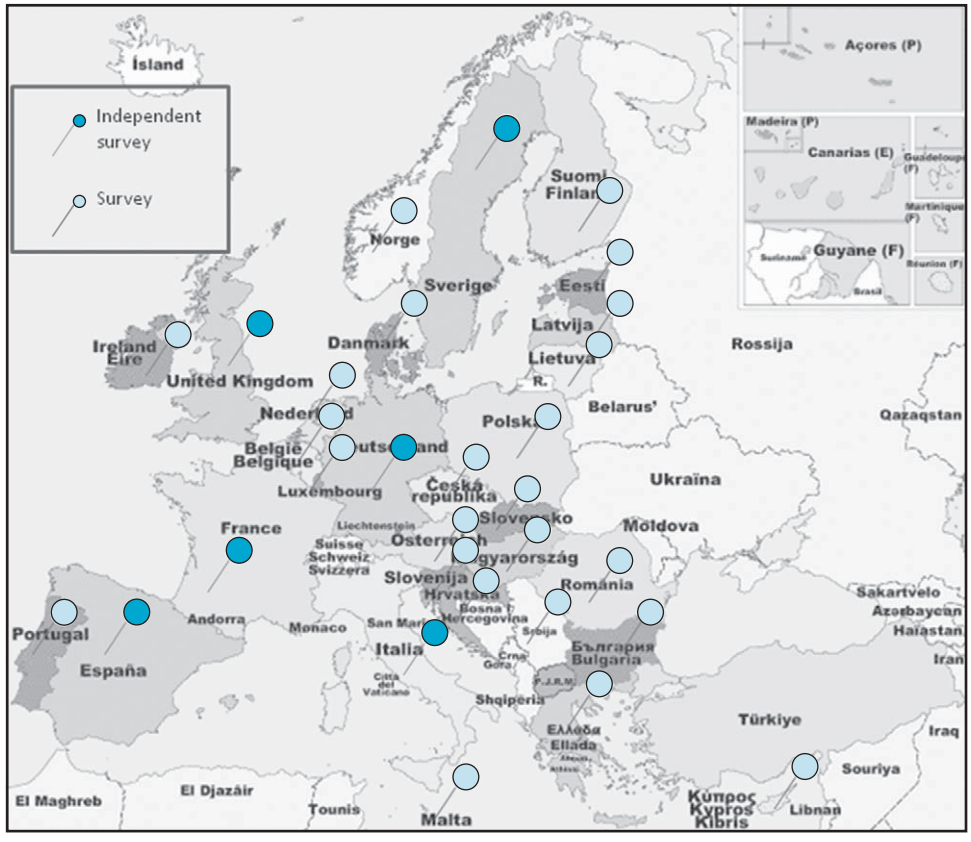

Fig. 1. Map of Europe with countries targeted for evaluation of the Infliximab Paediatric Crohn's Disease Educational Plan.

was to identify potential sources of potential prescribers. These included:

1. members of the Society for Pediatric Gastroenterology;[2]
2. paediatric hospitals from the Society of Children's Hospitals;[3]
3. clinics with paediatric wards offering gastroenterological care, as provided by the German Society for Children and Youth Medicine;[4]
4. internet search using key words 'gastroenterologische Ambulanz' (gastroenterological outpatient care) and 'Kinderklinik' (children's clinic).

A total of 152 physicians (paediatricians, gastroenterologists and paediatric gastroenterology specialists) were targeted for the survey using these sources.

In Germany, the response rate obtained from unsolicited telephone calls is generally low, and a mail survey was accordingly utilized to give physicians the opportunity to reply by fax. Questionnaires were mailed to the physicians in July 2008. Twenty-three physicians replied, of whom five did not treat paediatric Crohn's disease patients. The questionnaire was subsequently resent to all physicians who did not reply to the first mailing. A further 21 physicians replied and completed the questionnaire at this stage. Of these, five stated that they did not treat paediatric

2 Gesellschaft für Pädiatrische Gastroenterologie und Ernährung e.V. (http://www.gpge.de/).
3 Gesellschaft der Kinderkrankenhäuser (http://www.gkind.de/).
4 Deutschen Gesellschaft für Kinder- und Jugendmedizin (http://www.dgkj.de/).

Table I. Internal (sponsor's) staff and physicians identified by the independent survey or the sponsor

Country[a]	Employees from medical departments	Employees from marketing departments	Sales representatives	Targeted physicians	Questionnaires completed [n (%)]	Physicians treating PCD with infliximab who had the benefits and risks of infliximab explained to them by the sponsor's personnel [n (%[b])]
UK[c]	18[d]	0	23	50	53 (100)	11 (42)
Sweden	1	0	4[d]	41	32 (78)	14 (70)
Spain	4	1	45	39	28 (80)	22 (85)
France	9	1	24	96	55 (57)	44 (98)
Italy	11	5	42	169	91 (54)	60 (100)
Germany	8	2	15	152	43 (28)	11 (42)
Austria	2	2	5	8	8 (100)	8 (100)
Belgium[e]	16	12	8	34	24 (71)	17 (71)
Bulgaria	1	2	1	1	1 (100)	1 (100)
Croatia	2	2	1	6	6 (100)	5 (100)
Cyprus	1	NA[f]	1	3	0 (0)	NA
Czech Republic[g]	3	3	8	9	6 (67)	6 (100)
Denmark	3	1	3	12	9 (75)	9 (100)
Estonia[h]	2	1	1	2	2 (100)	1 (100)
Finland	4	4	7	22	20 (91)	16 (100)
Greece	3	6[i]	11	15	8 (53)	2 (100)
Netherlands	10	10	10	14	11 (79)	5 (45)
Hungary	2	2	2	15	13 (87)	10 (100)
Ireland	NA[j]	NA[j]	2	2	0 (0)	NA
Latvia	NA[k]	NA[k]	1	2	2 (100)	1 (100)
Lithuania	NA[k]	NA[k]	2	3	3 (100)	1 (100)
Luxembourg	NA[l]	NA[l]	NA[l]	1	1 (100)	1 (100)
Malta	1	NA	2	2	2 (100)	1 (100)
Norway	2	1	5	30	18 (60)	15 (83)
Poland	3	3	8	20	15 (75)	13 (100)
Portugal	2	2	7	8	3 (38)	3 (100)
Romania	2	2	12	3	3 (100)	3 (100)
Serbia	1	1	1	5	5 (100)	3 (100)
Slovakia	NA[m]	NA[m]	4	5	3 (60)	3 (100)
Slovenia	1	1	1	8	6 (75)	6 (100)

a Physicians in the UK, Sweden, Spain, France, Italy and Germany from the independent survey.

b Percentage of physicians currently treating PCD patients.

c Including Ireland.

d Including marketing personnel.

e Including Luxembourg.

f See Greece.

g Including Slovakia.

h Including Latvia and Lithuania.

i Including Cyprus and Malta.

j See UK.

k See Estonia.

l See Belgium.

m See Czech Republic.

NA = not applicable; **PCD** = paediatric Crohn's disease.

Crohn's disease patients. Finally, shortly after the second mailing, non-responders were contacted by telephone to increase participation in the survey. This yielded 9 further participants, making a total of 43 responding physicians in Germany.

France

In France, the selection process started by referring to the 2006 version of the Programme Médicalisé des Systèmes d'Informations (Medicalization Programme Information Systems).[5] This database was searched for centres where hospitalization of at least two different patients aged <18 years with a diagnosis of Crohn's disease had occurred. Eighty-four centres were identified. In addition to this, a further 23 teaching hospitals were also contacted.

The next step consisted of identifying paediatric, gastrointestinal disease and paediatric gastrointestinal disease wards in the identified hospitals. During July and August 2008, the wards were asked to confirm whether they did indeed have experience in paediatric Crohn's disease management, and the physicians managing these patients were identified.

Fifty-five interviews were performed by phone, mail or e-mail.

Italy

Selection of centres involved in the treatment of paediatric Crohn's disease patients in Italy was achieved by identifying 309 malattie infiammatorie croniche intestinali (chronic intestinal inflammatory disease) [MICI] centres. The MICI centres identified were then contacted by telephone. Forty-five percent (140 of 309 centres) did not treat paediatric Crohn's disease patients because they referred paediatric patients to the 16 regional centres in the country. The remaining 169 treating centres were telephoned and 91 interviews were completed.

Spain

In Spain, paediatric gastroenterology is not an officially recognized medical speciality. However, paediatricians who treat mainly gastroenterology patients are members of the Spanish Society for Paediatric Gastroenterology, Hepatology and Nutrition. A list of members of this Society was obtained (n = 57) and those who might have managed paediatric Crohn's disease patients were identified (n = 39).

A trained clinical research assistant contacted the physicians by phone at their hospital, and those physicians who agreed to partipate in the study were administered the questionnaire primarily by phone (two physicians asked to do so by e-mail and an electronic copy of the questionnaire was sent to them). Of the 39 physicians initially identified, 28 completed the questionnaire, one declined, and 10 did not respond.

Sweden

The Chairman of the Gastroenterology, Hepatology and Nutrition section of the Swedish Pediatric Society (SPS) was contacted during the start-up phase of the survey to enquire about the Society's interest in participating in this study in Sweden. The Chairman recommended contacting the hospital-based Clinic Managers listed on the SPS website (http://www.blf.net/vechadr.htm), since the Clinic Managers formally make the decision as to whether their staff should participate in activities requested by external bodies. No selection of hospitals was made. At hospitals with several paediatric clinics, the clinic caring for gastrointestinal disorders was identified. No honoraria was offered.

In the first round, the questionnaire was sent in June 2008 to 41 Clinic Managers listed on the SPS website. The Clinic Managers then distributed the questionnaire to the treating physicians. By early August 2008, 26 responses had been received and a reminder was sent to those physicians who had not responded. This reminder generated another six responses by mid-August 2008, giving 32 responses in total. Of these responses, seven came from university tertiary-care hospital clinics and 22

5 The Programme Médicalisé des Systèmes d'Informations is the national database on hospitalizations in France. It contains data on more than 18 million hospital stays and includes ambulatory stays (<2 days).

from secondary-care hospital clinics. The affiliation could not be determined for three respondents.

UK

Names and details of UK prescribers were obtained from a national medical database (www.specialistinfo.com) by searching for paediatric gastroenterologists *per se*, paediatricians with a special interest in gastroenterology, and gastroenterologists with a special interest in paediatrics. The search identified 170 physicians in the UK. The questionnaire was mailed out in batches to a sample of these prescribers, together with a covering letter, and respondents were asked to return the completed questionnaire within a 2-week period. Physicians could reply by mail in a reply-paid envelope, fax or e-mail, or be contacted by telephone for an interview if desired. Two batches of questionnaires were sent out: an initial batch of 60 questionnaires, followed by a further batch of 40 questionnaires 2 weeks later sent to initial non-responders to ensure that the required 50 responses were obtained. There was no further follow-up of non-responders.

Payment

Physicians were paid a fee for their participation according to the guidelines of each individual country.

Analysis

A descriptive analysis using frequency tables and graphics was performed. All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and STATA version 7.0 (StataCorp LP, College Station, TX, USA).

Results

Internal Evaluation of Sponsor's Staff

Training of internal staff was successfully provided to all selected personnel in all countries. Records of training were kept by the sponsor (see Appendix 1, Supplemental Digital Content).

Evaluation of the Educational Plan in Germany, France, Italy, Spain, Sweden and the UK

With the exception of Germany, the response rate to the survey in the six countries for whom independent organizations identified physicians treating paediatric patients with Crohn's disease was >50%; 78% in Sweden, 80% in Spain and 100% in the UK (table II). The lowest response rate was 28% in Germany, although ten of the identified physicians responded that they did not treat paediatric Crohn's disease patients, leading to a real response rate of 35% (53/152).

Ninety percent of the physicians were either paediatric gastroenterologists (57%) or paediatricians (33%). One physician from France did not identify his/her specialty, four physicians in Italy mentioned they had other specialties but did not specify what, and one physician in Sweden described himself as a paediatric oncologist.

Most (96%) of the surveyed physicians were currently treating paediatric Crohn's disease, which is to be expected since this was part of the screening performed during the selection process, and most gastroenterologists and paediatric gastroenterologists (82% overall) were currently using infliximab for the treatment of Crohn's disease. This proportion was lower among paediatricians (42%). Table III shows the percentage

Table II. No. of targeted physicians and response rate in the independent survey

Country	Physicians identified	Physicians targeted	Questionnaires sent	Questionnaires completed	Response rate (%)
Germany	152	152	152	43	28
France	96	96	96	55	57
Italy	169	169	169	91	54
Spain	39	39	35	28	80
Sweden	41	41	41	32	78
UK	170	50	100	53	100

Table III. No. and percentage of interviewed physicians currently treating paediatric Crohn's disease patients with infliximab, stratified by specialty and country

Country	Paediatric gastroenterologists [n (%)][a]	Gastroenterologists [n (%)][a]	Paediatricians [n (%)][a]
Germany	18 (78)	1 (100)	7 (37)
France	30 (91)	7 (70)	8 (73)
Italy	40 (75)	10 (77)	10 (48)
Spain	21 (95)	NA	5 (83)
Sweden	12 (80)	0 (0)	8 (53)
UK	22 (85)	NA	4 (15)

a Denominator is number of physicians currently treating paediatric Crohn's disease with any drug.

NA = not applicable.

of physicians of each specialty and country who treat paediatric Crohn's disease with infliximab.

Ninety-six percent of paediatric gastroenterologists or gastroenterologists declared themselves aware of the benefits and risks of using infliximab for the treatment of Crohn's disease; fewer paediatricians (82%) declared themselves aware of the benefits and risks. The majority initially gained awareness through attendance at congresses and workshops, and at the time of the survey only 24% declared that they had become aware of the benefits and risks through the educational programme. A further 26% gained awareness through direct calls to company representatives (figure 2).

Prior to the survey, the majority of physicians reported they had been approached by MAH personnel in connection with prescription of infliximab in France (98%), Italy (100%), Spain (83%) and Sweden (70%). In Germany and the UK this proportion was lower (both 42%).

Almost all physicians (figure 3) reported being aware of the need to perform TB and cancer screening prior to initiating therapy with infliximab, and to screen for hypersensitivity reactions before, during and after treatment. Ten percent of the physicians were not aware of the need to update immunization before initiating therapy and, except in Italy (92%), around 50% of the physicians were not aware of the need to provide patients with the infliximab Patient Alert Card (see Patient Alert Card, Supplemental Digital Content).

By specialty, gastroenterologists were more aware of the risks and benefits of infliximab for paediatric Crohn's disease, and used the Patient Alert Card more than paediatricians and paediatric gastroenterologists.

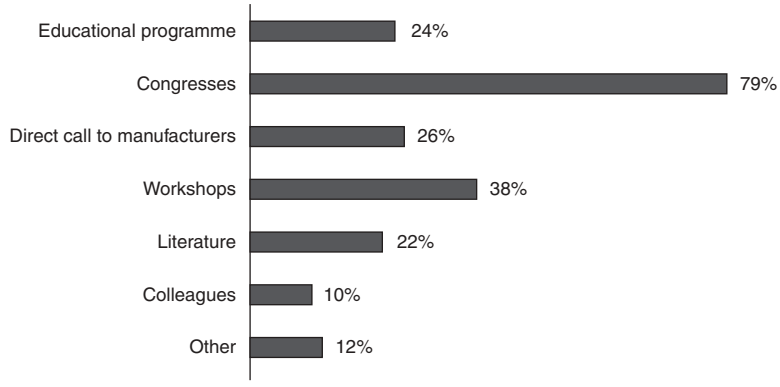

Fig. 2. Sources creating awareness of the benefits and risks of infliximab identified by physicians interviewed in the UK, Germany, Sweden, Italy, France and Spain in 2008.

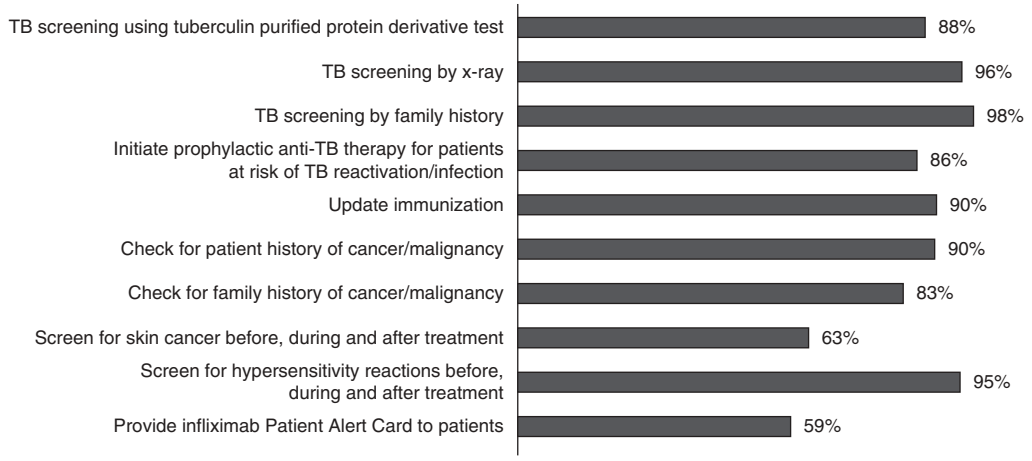

Fig. 3. Percentage of physicians in the UK, Germany, Sweden, Italy, France and Spain interviewed in 2008 reported to be aware of the need to perform the actions shown prior to initiating therapy with infliximab in patients with paediatric Crohn's disease. **TB** = tuberculosis.

Evaluation of the Educational Plan in other Countries

Of the other European countries surveyed, in all countries except Ireland, Cyprus and Portugal, more than half of the physicians contacted responded (table I). None of the physicians targeted in Ireland and Cyprus responded. With the exception of Belgium, where 50% of the physicians interviewed were gastroenterologists, the vast majority of physicians were specialized in paediatric gastroenterology or paediatrics. Most (86%) of the physicians treated paediatric Crohn's disease patients and most of these physicians (85%) reported that they were currently treating this disorder with infliximab.

Ninety-nine percent of paediatric gastroenterologists and 90% of gastroenterologists or paediatricians declared themselves aware of the benefits and risks of using infliximab for the treatment of Crohn's disease. The majority first gained awareness through congresses (92%) or communication with the sponsor's personnel (69%). All physicians reported they were aware of the risk of TB and opportunistic infections and the need to perform TB and cancer screening prior to initiating therapy with infliximab. All physicians were aware of the risk of hypersensitivity reactions. Ninety-six percent (162/169) of the physicians were aware of the risk of hepatosplenic T-cell lymphoma reported with use of infliximab and azathioprine and/or mercaptopurine as concomitant treatment.[27]

As in the independent survey, 10% of the physicians were not aware of the need to update immunization before initiating therapy, and 30% of the physicians were not aware of the need to provide patients with the infliximab Patient Alert Card.

Discussion

This article presents the results of an evaluation of the effectiveness of an educational programme aimed at personnel from the MAH and prescribers of infliximab for the treatment of paediatric Crohn's disease. Risk management as applied to therapeutic agents has become widespread over the last 10 years. One part of risk minimization is the use of educational activities, which is a well established way of promoting, preserving and restoring public health.[4,5]

The European Medicines Agency has endorsed the use of targeted educational programmes as an important means of informing healthcare providers and patients about the risks of a particular therapeutic agent.[28] Assessments of drug safety risk comprehension should be performed. It is recommended that direct measurement of the

effectiveness of risk minimization should be undertaken whenever feasible. Measures based on the provision of information to professionals, or descriptive studies and surveys that assess if the information is being effectively communicated, are considered appropriate.[28]

This study assessed the effectiveness of the educational efforts conducted by the infliximab MAH in six of the most populated countries in Europe using a survey for which the prescribers were identified independently of the MAH. In these countries, infliximab was used by most (82%) paediatric gastroenterologists or gastroenterologists to treat paediatric Crohn's disease. On the other hand, only 42% of paediatricians treated paediatric Crohn's disease with infliximab. The reason for this difference is unknown. The percentage of self-reported awareness of the benefits and risks of using infliximab for the treatment of Crohn's disease was very high for paediatric gastroenterologists or gastroenterologists (96%), with a slightly lower proportion among paediatricians (82%).

Overall, it seems that the educational efforts included in the infliximab RMP are working. While most physicians (79%) received information on the risks associated with infliximab through congresses, 24% became aware directly as a result of the educational programme, and a further 26% became aware by contacting an MAH representative directly. Most physicians surveyed reported that they had been approached by the sponsor's personnel to discuss the risks associated with infliximab in the paediatric Crohn's disease population in France (98%), Italy (100%), Spain (83%) and Sweden (70%). In Germany and the UK this proportion was lower (42% in each country). This inconsistent result on the role of the sponsor in the education of the physicians is difficult to interpret as the degree of availability of physicians is variable, as was their cooperation in the survey.

Most physicians surveyed reported being aware of the risks associated with infliximab use, as specified in the RMP; however, the degree of awareness was not homogeneous among prescribers in different countries in Europe. Germany and the UK seem to be the countries where more follow-up efforts regarding education are needed. Almost all physicians were aware of the need to perform TB and cancer screening prior to initiating therapy with infliximab, and to screen for hypersensitivity reactions before, during and after treatment. However, 10% of the physicians were not aware of the need to update immunization before initiating therapy and, except in Italy (92% aware), around 50% of the physicians were not aware of the need to provide patients with the infliximab Patient Alert Card. This relatively low use of the Patient Alert Card may reflect different perceptions of this tool by those involved in risk management. While regulatory authorities may perceive the Patient Alert Card as an important information tool, some prescribers may see it as cumbersome and loaded with information that the patient may have difficulty comprehending or putting into perspective. This unexpected low use of an obligatory tool has also been described when evaluating factors influencing staff enforcement of pupils' smoking restrictions; 66% of schools did not implement the programme properly, and between 65% and 79% of teachers did not implement the programme properly or did so while omitting programme components.[29]

Like any other study, the current study has limitations. One is that participation in the survey was voluntary. It is possible that those who participated were more compliant with the risk minimization tools than those who did not participate. Prescribers were paid a small fee according to each country's guidelines to improve compliance, and it is also possible that payment of the fee may have introduced a bias that is essentially impossible to ascertain or measure.[30] The information provided was self-reported and may 'paint a better picture' than what is happening in reality. In the absence of a tool to monitor physician behaviour, it is impossible to determine whether this bias actually exists or to determine its importance. The importance of this potential bias may be even greater where the survey was conducted on a list of prescribers obtained directly from the sponsor. However, the disease is rare and the drug is used by a small sample of physicians in each country, which

increases the representativeness of the survey. Another limitation was that the questionnaire itself was not validated before being used, which may have resulted in some degree of bias.[31] The evaluation of evidence must distinguish between the accuracy of the evaluation process in detecting the success or failure of an intervention, and the success or failure of the intervention itself.[32] Furthermore, it was impossible to evaluate the effect of the educational programme in two EU countries (Cyprus and Ireland) since no completed questionnaires were received from those two countries. Finally, while training records are valuable for documentation of the occurrence of training sessions, they may not provide meaningful information about the effectiveness of the session.

In the authors' experience, when conducting surveys in the EU, it is important to maintain as much consistency in methodology as possible across the countries involved while retaining sufficient flexibility to allow for the idiosyncracies of each country. In this case, the questionnaire used was common to all of the six most heavily populated countries and the differences between the questionnaire used in these six and the remaining countries were minimal. On the other hand, in Germany, for example, unsolicited telephone calls are not considered appropriate and a mail survey was therefore employed, whereas in other countries, such as Italy or Spain, unsolicited telephone calls are acceptable. In some countries, for example France, it was possible to search a database as the first step in identifying possible treating physicians, whereas this step was unavailable in other countries. In Sweden it is important to involve Clinic Managers in surveys, since they formally make the decision as to whether their staff should participate in activities suggested by external bodies. In some countries, such as the UK, lists of physicians by specialty are available, while in others it is best to use information provided by professional societies.

Conclusions

This study shows that the internal (sponsor's) educational programme was completed satisfactorily. An independent survey was performed successfully among physicians in six of the most populated European countries, and over 90% of the physicians surveyed declared themselves aware of the risk and benefits of infliximab. However, the perceived value of the Patient Alert Card, seen as a cornerstone of medical education by regulators, may not be shared by physicians. Efforts directed at increasing participation and representativeness in evaluation of risk minimization activities are needed.

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