

Concise report

ImmunoStart: preparing patients for immunosuppression

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Abstract

Objectives. Patients with immune-mediated inflammatory disease (IMID) present an increased risk of infection. Here, we present the concept of a preventive consultation called ImmunoStart and the first results of its implementation in the care pathway of patients with IMID.

Methods. Relevant information about vaccination history, tuberculosis exposure and other infectious risks were collected through blood sampling, complete anamnesis, chest X-ray and Mantoux test. During the ImmunoStart consultation, vaccination schedules, specific treatments and risk considerations were discussed.

Results. Between October 2016 and February 2020, 437 patients were seen at an ImmunoStart consultation, mainly referred by rheumatologists (56%), dermatologists (25%) and gastroenterologists (18%). A total of 421 (96%) patients needed at least one vaccine (a mean of 3.3 vaccines per patient). Live attenuated vaccine was indicated for 45 patients (10%), requiring them to reduce or interrupt their immunosuppressive drug(s). Ninety-two patients (21%) were treated for latent tuberculosis infection.

Conclusion. This preventive consultation provides a centralized and systematic setting for the direct management of patients with IMID in need of vaccination, treatment of latent disease and specific advice regarding their immunomodulating treatments.

Key words: immune-mediated inflammatory disease, prevention, immunosuppression, vaccination, screening, latent

Key messages

- Screening and vaccinations in patients with immune-mediated inflammatory disease should ideally take place before starting an immunomodulating treatment.
- A centralized setting allows all patients with immune-mediated inflammatory disease to be referred systematically for this complete preventive management.
- A concept such as the ImmunoStart consultation makes it possible to carry out screenings and vaccinations in optimal conditions.

Introduction

Immune-mediated inflammatory diseases (IMIDs) are multifactorial systemic diseases with aberrant immune

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responses. Treatment is currently based on conventional synthetic DMARDs (csDMARDs) and, in cases of treatment failure, on biological DMARDs (bDMARDs), biosimilar DMARDs (bsDMARDs) or targeted synthetic DMARDs (tsDMARDs). Patients with IMID bear an increased risk of infections owing to the immunosuppressive effect of the underlying disease and the use of immunomodulatory medication to treat the IMID. The incidence and severity of infections are higher in patients with IMIDs, including the incidence of vaccine-preventable infections [1–4]. In the last decade, many new b/bs/tsDMARDs have been developed for IMID patients, and an increasing number of indications are being recognized for their use. Moreover, they are used earlier in the course of IMID [5]. International guidelines recommend screening for latent tuberculosis infection (LTBI) before prescription of a TNF- α blocker [6, 7]. Guidelines for vaccination of patients with IMID [5, 8], including recently updated Belgian guidelines [9], are also available, but several reports point out low adherence [10, 11]. The main reasons for low adherence to vaccination are concerns about vaccine safety and lack of clarity about who is in charge of the screening and vaccination of the patient [10].

MTX and CSs, but also abatacept and some TNF- α blockers have shown deleterious effects on the immune response after vaccination with inactivated vaccine, at least for primary vaccination [8, 12]. Live attenuated vaccines are contraindicated during immunosuppressive therapy owing to the risk of disease from the live attenuated pathogen [12, 13]. Finally, latent infections other than *Mycobacterium tuberculosis* can also reactivate during specific immunomodulating treatments, such as occult hepatitis B [1] or shingles (varicella zoster virus reactivation). Therefore, there is a need for specific screening, for vaccinations and for targeted advice in patients with IMID, ideally before starting an immunomodulating treatment.

Given that it is challenging for IMID specialists to manage this pre-therapeutic assessment together with the disease therapy plan, a joint care programme between IMID specialists (mainly gastroenterologists, rheumatologists, and dermatologists) and infectious disease specialists has been created in our hospital and called the ImmunoStart consultation. ImmunoStart is led by a specialist in infectious diseases, with the aim to ensure a targeted screening, counselling and vaccination programme for each patient with IMID. This consultation is planned as soon as possible after IMID diagnosis. In this paper, we present the data from this innovative ImmunoStart consultation.

Methods

The Centre Hospitalier Universitaire Saint-Pierre (CHU Saint-Pierre) in Brussels is a tertiary public hospital. Specialists in gastroenterology, rheumatology and dermatology of CHU Saint-Pierre created the Biologic Platform, an outpatient clinic welcoming ~200 new patients with IMID per year. Patients are followed-up prospectively, treated with standard of care and/or

enrolled in therapeutic clinical trials, and their data are centralized in a database after having signed an informed consent. All adult patients (primarily new patients) are referred to the ImmunoStart consultation as soon as possible even if they are already being treated with an immunomodulating drug. Patients with a flare-up of their disease or patients who have already undergone a vaccinal work-up and already been screened for LTBI are not (immediately) addressed to the consultation. The following serological analyses are performed before the ImmunoStart consultation: hepatitis A, B and C, *Treponema pallidum*, measles, rubella (women only), varicella, HIV, and sometimes *Trypanosoma cruzi* and *Strongyloides stercoralis* if the patient originates from an endemic area. An IFN- γ -release assay is performed. If HBsAg or HBcAb (without HBsAb) is positive, HBV DNA is measured. Chest X-ray (with or without chest CT if X-ray is abnormal) and Mantoux test are performed before the ImmunoStart consultation.

During the ImmunoStart consultation, medical history, former and current treatment, country of birth, travel history and plans, immunization history, tuberculosis contact history and household composition are reviewed with the patient. According to the serological status, and following the recommendations of national and international guidelines [9, 14], the following vaccines can be proposed: diphtheria/tetanus/acellular pertussis combined vaccine (dTap), inactivated polio vaccine, measles/mumps/rubella combined vaccine (MMR), quadrivalent conjugated meningococcal vaccine, B meningococcal vaccine, conjugated and/or polysaccharidic pneumococcal vaccine, quadrivalent inactivated influenza vaccine, hepatitis B vaccine, varicella vaccine, zoster vaccine and papillomavirus vaccine. If the patient has travel plans, hepatitis A vaccine, yellow fever (YF) vaccine, inactivated typhoid vaccine and rabies vaccine can be proposed. If LTBI screening test is positive, treatment is started, and the patient is followed to ensure adherence and tolerance until completion of treatment. Ivermectin 200 μ g/kg single dose is administered during the ImmunoStart consultation of patients originating from hyperendemic areas for *S. stercoralis*, regardless of the serology result. Household vaccination, frequency of gynaecological and/or dental follow-up, specific preventive measures against *Listeria monocytogenes*, *Legionella pneumophila*, travel-related diseases or other specific risks are discussed with the patient during consultation.

All patients' data and administered vaccines and drugs are entered into a specific ImmunoStart database (REDCap Research Electronic Data Capture, v.8.6.0). We used descriptive statistics to summarize the characteristics of our population. Hypothesis tests for differences between groups were performed using non-parametric Wilcoxon–Mann–Whitney and Kruskal–Wallis tests for continuous variables, and Fisher exact tests for our categorical variables. All our *P*-values are bilateral and considered statistically significant if <0.05 . We used SAS statistical software (v.9.4; SAS institute, Cary, NC, USA). The Ethical Committee of CHU Saint-Pierre approved this study (CE/20–07–06).

TABLE 1 Summary of the characteristics of the patients attending ImmunoStart consultation ($n = 437$)

Characteristic	Value
Female sex	240 (55)
Age, median (interquartile range), years	44 (34–55)
Birth region	
Western Europe	217 (50)
Eastern Europe	34 (7.8)
North Africa	97 (22)
Sub-Saharan Africa	36 (8)
Central and South America	23 (5.2)
Asia	28 (6.4)
North America	2 (0.5)
Lived >10 years in another country	272 (62)
Lived >10 years in region	
Western Europe	43 (16)
East Europe	34 (12.5)
North Africa	94 (34.6)
Sub-Saharan Africa	43 (15.8)
Central and South America	24 (8.8)
Asia	33 (12.1)
North America	2 (0.7)
HIV infection	12 (2.4)
History of close contact with somebody diagnosed with tuberculosis	83 (19)
Do not live alone	336 (77)

Values are given as n (%) unless stated otherwise.

Results

Between October 2016 and February 2020, 437 patients attended the ImmunoStart consultation (70 in 2017, 193 in 2018, and 162 in 2019). They were mainly referred by rheumatologists (56%), dermatologists (25%) and gastroenterologists (18%) and followed up for RA (23%), cutaneous psoriasis (20%), PsA (18.5%), AS (15%) and Crohn's disease (13%). Patient characteristics are summarized in Table 1.

Forty-four percent of patients had already started an immunomodulating treatment before attending the ImmunoStart consultation. Two-thirds of the cohort (67%) had travelled or were planning to travel to tropical areas, 62% of whom planned to travel to yellow fever endemic zones.

After checking the serological status and vaccination history, 1380 vaccines were administered to 421 patients (96%) in the context of the ImmunoStart consultation (mean of 3.3 vaccines per patient).

Patients with indication for live attenuated vaccines (measles, varicella and yellow fever)

A total of 140 live attenuated vaccines (43 MMR, 89 YF vaccines and 8 varicella vaccines) were administered

TABLE 2 Diagnosis of latent tuberculosis infection (positive Mantoux and/or positive IFN- γ -release assay and/or never-treated tuberculosis sequelae on thoracic CT)

LTBI test	Total number	Number positive (% of total cohort)
Mantoux	383	73 (19)
IFN- γ -release assay	412	59 (14)
Lung CT	53	17 (32)
LTBI diagnosis	437	108 (25)
LTBI treatment		92 (21)

Mean skin induration in positive Mantoux tests was 12 mm. LTBI: latent tuberculosis infection.

during the ImmunoStart consultation: 45 of 437 patients (10%) had to reduce or discontinue their immunosuppressive drugs to allow safe administration of live attenuated vaccines. No side-effects were observed after the administration of these live attenuated vaccines. Among the cohort, 24 patients (5%) had an indication for administration of one or more live attenuated vaccine but presented a formal contraindication because of the treatment with immunosuppressive drug(s). A total of 55 patients (13%) had negative IgG for measles. Of these, 49% were born in Western Europe. Patients <45 years old were more likely to need measles vaccine ($P = 0.0001$). The majority of patients (415 of 437, 95%) were tested positive for varicella zoster virus IgG. Patients planning to travel to yellow fever endemic areas ($n = 182$) and needing yellow fever vaccine were more likely to be <45 years old ($P < 0.0001$) and were less likely to have spent their childhood abroad ($P = 0.08$).

Patients with indications for inactivated vaccines

During the ImmunoStart consultation, 65% of the patients received a combined diphtheria-tetanus-acellular pertussis vaccine. Patients >45 years of age and originating from North Africa were more likely to need a tetanus booster ($P = 0.035$). Fifty (17%) of future travellers to tropical areas had negative hepatitis A IgG. Patients <45 years old and born in Western Europe were more likely to need hepatitis A vaccine ($P < 0.0001$). Hepatitis B vaccines were administered to 41 patients in the population at risk for this disease. Two hundred and thirty-one patients (53%) were vaccinated against influenza, and 259 patients were administered pneumococcal vaccine during the ImmunoStart consultation.

Screening for latent tuberculosis infection

Table 2 summarizes the results of LTBI screening in our cohort. At least one of the three LTBI tests was positive in 108 patients (25%). Risk factors for having at least one LTBI-positive test were male sex ($P = 0.007$), being born or having lived during childhood in Sub-Saharan Africa, Eastern Europe or North Africa ($P = 0.0021$,

$P=0.0032$ and $P=0.0008$, respectively) and reporting a close contact with somebody diagnosed with tuberculosis ($P=0.046$).

Other screenings

Forty-six patients (10.6%) originated from hyperendemic zones for *S. stercoralis*, including 36 who were scheduled to receive CSs, who were treated to prevent *S. stercoralis* reactivation. Four patients (0.9%) were started with hepatitis B reactivation prophylaxis.

Discussion

A large majority (96%) of patients who attended the ImmunoStart consultation needed at least one vaccine. A significant proportion of patients (10%) had to manage a break or reduction in their immunomodulating treatment to receive live attenuated vaccines. Finally, one in every five patients was treated for LTBI. These results stress the high relevance of preventive consultations, such as ImmunoStart, ideally before starting immunosuppression, to facilitate and ensure the quality of future care for IMID patients. CHU Saint-Pierre is a centrally located public hospital in Brussels, accounting for the great diversity in countries of origin of patients. Therefore, in the context of the ImmunoStart consultation, a large number of patients originate from countries endemic for *M. tuberculosis*, HBV or *Strongyloides*, for example, highlighting the importance of a robust prevention strategy.

In our experience, 10% of patients had to manage a decrease or a break in their immunomodulating drugs in order to receive a live attenuated vaccine, which could have been avoided if the patient had had a vaccination check-up before starting the immunomodulating drugs. Moreover, the recommendations regarding withdrawal times for immunomodulating drugs, often based on expert opinion rather than on evidence-based or clinical trials, differ greatly from one guideline to another [8, 14]. To address this issue, the recent Belgian guidelines were designed to be as adaptable as possible (based on the half-life of immunomodulating drugs) and make it possible to derive a rule applicable to all drugs, past or future [9]. Nonetheless, administration of live attenuated vaccines is challenging in IMID patients. For example, a contraindication to yellow fever vaccination may hamper the possibility for patients to travel (including to visit their families) to yellow fever endemic areas. Concerning measles-containing vaccine, younger patients born in Western Europe were more likely to test negative for measles IgG. This might be explained by the very low circulation of the measles virus in Western Europe (in Belgium since the 1970s), in contrast to countries outside Western Europe and in developing countries. Outbreaks of measles in Belgium and in several European countries have been observed in recent years [15]. This highly infectious disease can potentially be severe in immunocompromised patients [4]. Moreover,

access to post-exposure prophylaxis for measles is complicated and extremely expensive in Belgium. Therefore, it is particularly important to target young patients born in industrialized countries for measles IgG screening before starting immunomodulatory drugs.

Hepatitis A can be severe in immunocompromised patients, and primary vaccination against HAV during administration of immunomodulating drugs has been associated with a high rate of vaccine failure [16]. It is therefore also strongly recommended to check the generation of IgG after vaccination and/or to apply one of the recently described high-dose vaccination regimens [17]. From 2021 onwards, the ImmunoStart consultation has also provided an opportunity to discuss and propose a vaccination schedule against severe acute respiratory syndrome coronavirus 2 that was best suited to each patient.

Given that most IMID patients will benefit from TNF- α blockers at some point in their disease, we performed the same LTBI screening for all patients attending the ImmunoStart consultation. At the ImmunoStart consultation, we diagnosed LTBI according to the either positive strategy [6, 18]. Probably owing to the multicultural nature of our cohort, a high proportion of patients were positive to one of the screening tests. However, this proportion might still be underestimated given the high number of patients already treated with immunosuppressive drugs, which is known to alter the results of LTBI screening [19, 20]. If screening for tuberculosis infection is to be targeted more precisely, it should focus primarily on male patients, those who were born or have lived abroad, or those who report having had close contact with a tuberculosis patient, and preferably, should be carried out before starting immunomodulatory therapy.

Our study has limitations. It should be noted that almost half of the patients of this cohort were already on immunomodulating treatment at the time of the ImmunoStart consultation, and that physicians in some specialties refer patients more systematically than others. Although it is not perfect, the history, the consultation of vaccination records and the serological analyses make it possible to assess the vaccination needs of each patient with reasonable accuracy. To our knowledge, this is the first time that the characteristics of a cohort of patients seen in such a centralized consultation have been reported. Importantly, the ImmunoStart consultation allows infectious disease physicians to acquire expertise in a constantly evolving field and IMID physicians to have a reference infectious disease physician for the management of these complex patients. In conclusion, ImmunoStart consultations provide a centralized and systematic setting for the prevention of infectious complications in patients with IMID.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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